ARCHIVES of INTERNAL MEDICINE

VOLUME 65 MARCH 1940 NUMBER 3

COPYRIGHT, 1940, BY THE AMERICAN MEDICAL ASSOCIATION

TOXIC HEPATITIS

INTERMEDIARY FATAL FORM WITH ENLARGEMENT OF THE LIVER; A CLINICAL AND PATHOLOGIC STUDY

J. D. KIRSHBAUM, M.D.

AND

H. POPPER, M.D.*

CHICAGO

Toxic hepatitis is known to both clinician and pathologist. Pathologists know the fatal form, acute yellow or red atrophy, characterized grossly by the small atrophic liver and microscopically by necrosis of the liver cells. Clinicians are more familiar with a nonfatal form of hepatitis, of which so-called catarrhal jaundice is typical. In cases of the latter condition the liver is usually enlarged, and since recovery is the usual outcome, knowledge of the pathologic changes is meager, except for a few histologic descriptions which are available from biopsies of the liver or from autopsy in cases of accidental death (Klemperer,[1] Schrumpf,[2] Popper,[3] Eppinger and his associates[4] and Aschoff[5]).

Eppinger[6] was the first to state that catarrhal jaundice is the miniature form of acute yellow atrophy. The few histologic observations available confirm the statement, later supported by Gaskell,[7] Boyd[8] and others. Animal experiments with allylformiate intoxication by Popper[9] have revealed the transition from catarrhal jaundice to acute atrophy of the liver.

* Research Fellow in the Cook County Graduate School of Medicine.

From the Department of Pathology of the Cook County Hospital and the Cook County Graduate School of Medicine.

1. Klemperer, P.; Killian, J. A., and Heyd, C. G.: Pathology of "Icterus Catarrhalis," Arch. Path. **2**:631 (Nov.) 1926.
2. Schrumpf, A.: Ann. d'anat. path. **9**:17, 1932.
3. Popper, H.: Ztschr. f. klin. Med. **131**:161, 1937.
4. Eppinger, H.; Kaunitz, H., and Popper, H.: Die seröse Entzündung, Berlin, Julius Springer, 1935.
5. Aschoff, L.: Verhandl. d. deutsch. Gesellsch. f. inn. Med. **44**:261, 1932.
6. Eppinger, H.: Die Leberkrankheiten, Berlin, Julius Springer, 1937.
7. Gaskell, J. F.: J. Path. & Bact. **36**:257, 1933.
8. Boyd, W.: The Pathology of Internal Diseases, ed. 2, Philadelphia, Lea & Febiger, 1936.
9. Popper, H.: Wien. klin. Wchnschr. **49**:207, 1936.

It is natural, then, to ask what causes the enlargement of the liver in catarrhal jaundice and how the contrast to the smallness of the liver in acute yellow atrophy may be explained.

This question prompted our study of a group of 15 cases in which jaundice was fatal. The liver was observed to be enlarged at autopsy, as in catarrhal jaundice, whereas the clinical picture was that of an acute fulminating hepatic disease, with death occurring within a short time, as in cases of acute yellow atrophy of the liver. In a review of the literature and modern textbooks of medicine, one fails to find a thorough description of cases such as ours.

In addition to the reported cases of typical catarrhal jaundice mentioned previously, we have found reference to cases similar to ours in the textbook of Eppinger,[6] who reviewed 63 cases of clinical acute yellow atrophy. Of this group, he classified 17 as instances of catarrhal jaundice. Histologically, there were 1 case of diffuse serous hepatitis with dissociation, 12 cases of central necrosis, 1 case of peripheral necrosis and 3 cases of fatty degeneration similar to that in phosphorus poisoning. In this series of cases no mention is made of the size of the liver, whether it was enlarged or shrunken.

In 1932 the late Dr. Jaffé [10] called attention to a case of acute toxic hepatitis characterized by jaundice of two weeks' duration. At autopsy enlargement of the liver was noted, and microscopic examination showed marked separation of the liver cells and cloudy swelling. From 1929 to 1939, in a series of 12,000 consecutive autopsies at the Cook County Hospital, 15 cases of acute toxic hepatitis with enlargement of the liver were encountered. Excluded from this group were cases of poisoning from drugs, such as arsphenamine and mercury, and cases in which toxic hepatitis was secondary to other conditions, e. g., pneumonia and suppurative processes.

CLINICAL OBSERVATIONS

In our group there were 10 males and 5 females; 6 of the males and 1 of the females were Negroes; the youngest was 10 years of age, the oldest 58. The average duration of illness was nine and a half days, the shortest one day and the longest twenty-one days; in addition, 2 patients had been ill two months and three months, respectively.

Ten patients had symptoms of sudden onset, with chills, fever, vomiting, abdominal pains and jaundice. This was followed by stupor and unconsciousness. Headaches were a frequent complaint. Anuria, which usually occurs with acute yellow atrophy, was observed in 2 patients. Six patients complained of pains in the joints and muscles.

Two of the patients had active gonorrhea and 1 latent syphilis. In 2 there was evidence of disease of the gallbladder two years prior to admission. In 2 patients meningeal symptoms predominated; in 1 of

10. Jaffé, R. H.: Bull. Chicago M. Soc. **35**:312, 1932.

them meningitis was suspected because of the pains in the neck and slight rigidity, but the result of a spinal puncture proved negative.

The diagnosis of acute primary hepatitis was made in 8 cases, while in 1 infectious hepatitis was considered. In 4 cases a mechanical type of jaundice was suggested; in 2, gallstones, and in the other 2, cholecystitis and carcinoma of the liver. In 2 cases uremia was suggested; however, in 1 instance the diagnosis of hepatitis was made prior to death. In 1 the condition was considered to be biliary cirrhosis.

Alcoholism was observed in 2 cases, and paratyphoid B bacilli were isolated from the blood and feces of the child.

The laboratory examination was not always complete, because many of the patients died shortly after admission. The blood showed moderate anemia; the average red cell count was 3,710,000 per cubic millimeter, but it was not characteristic. The white cell count was always high, varying from 11,000 to 38,200 per cubic millimeter. The icteric index varied from 90 to 250, the rise being usually rapid, within a few days. The urea nitrogen varied from 40 to 205 mg. per hundred cubic centimeters of blood. In 3 patients the creatinine of the blood fluctuated from 6.66 to 16 mg. per hundred cubic centimeters. The Wassermann reaction of the blood was negative in 5 cases, while in 1 there was anatomic evidence of syphilis and in another the Wassermann reaction of the spinal fluid was positive; in 8 cases the blood was not examined. Examination of the urine showed albuminuria, bilirubinuria and casts in the sediment. The stools were examined in 11 cases; in 6 they were clay colored, in 3 green to brown and in 2 tarry.

The temperature varied from 99.6 to 105 F. In 12 cases there was tachycardia (with a rate of from 96 to 135), while in 1 bradycardia (with a rate of 68) was present. The blood pressure was usually low, the systolic varying from 85 to 134 and the diastolic from 52 to 80. Enlargement of the liver was noted in 10 cases, and the spleen was palpated in 5.

ANATOMIC OBSERVATIONS

The liver was enlarged. In the 14 adults the weight varied from 1,480 to 3,640 Gm., the average being 2,150 Gm. The weight of the child's liver was 950 Gm. There was no correlation between the acuteness of the illness and the degree of enlargement of the liver. The capsule was tense; the edges were round; the consistency was firm, and the cut surface was usually grayish brown. The gallbladder in 4 cases showed fibrosis, while in 1 there were stones in the lumen, and in 1 a cholecystectomy had been done. In all cases the extrahepatic bile ducts were free and showed no changes.

The spleens varied in weight from 90 to 690 Gm., with an average of 253 Gm. The weight of the spleen of the child was 200 Gm. The spleen was soft in 11 cases.

The heart was hypertrophic in 4 cases and dilated in 3.

The kidneys were usually markedly swollen, the weight varying from 360 to 660 Gm., with an average of 490 Gm. The lungs showed edema in 8 cases; there was catarrh of the gastric mucosa in 2 cases and of the intestine in 5. In only 3 of them was there slight ascites, the fluid

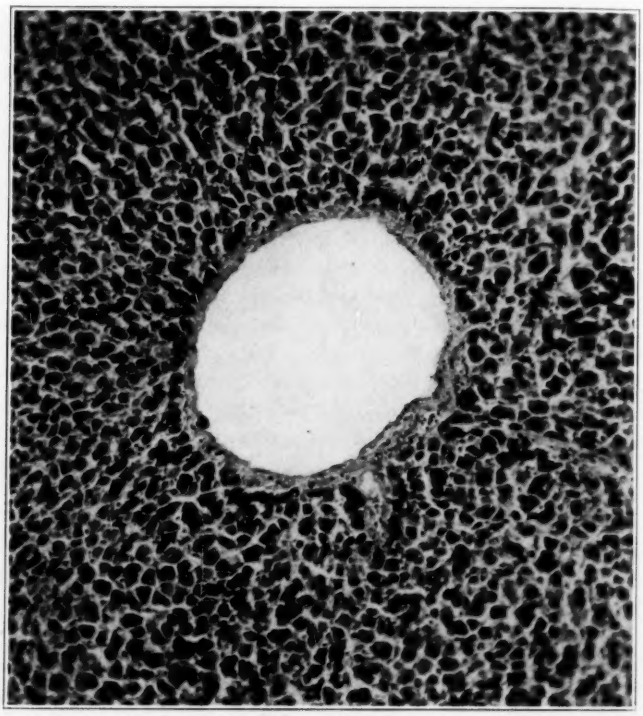


Fig. 1.—Note the dissociation of the cords of liver cells about a central vein and the normal-staining nuclei (low magnification).

measuring up to 150 cc. In 11 instances there were signs of hemorrhagic diathesis, especially in the skeletal muscles in 2.

In all 15 cases jaundice was marked.

HISTOLOGIC OBSERVATIONS

Thorough histologic studies were made in 13 of the cases. The outstanding observation was moderate to marked interruption of the cords of liver cells, separating single cells or groups of cells (fig. 1). The free edges of the cells in the groups showed rounding, and as the

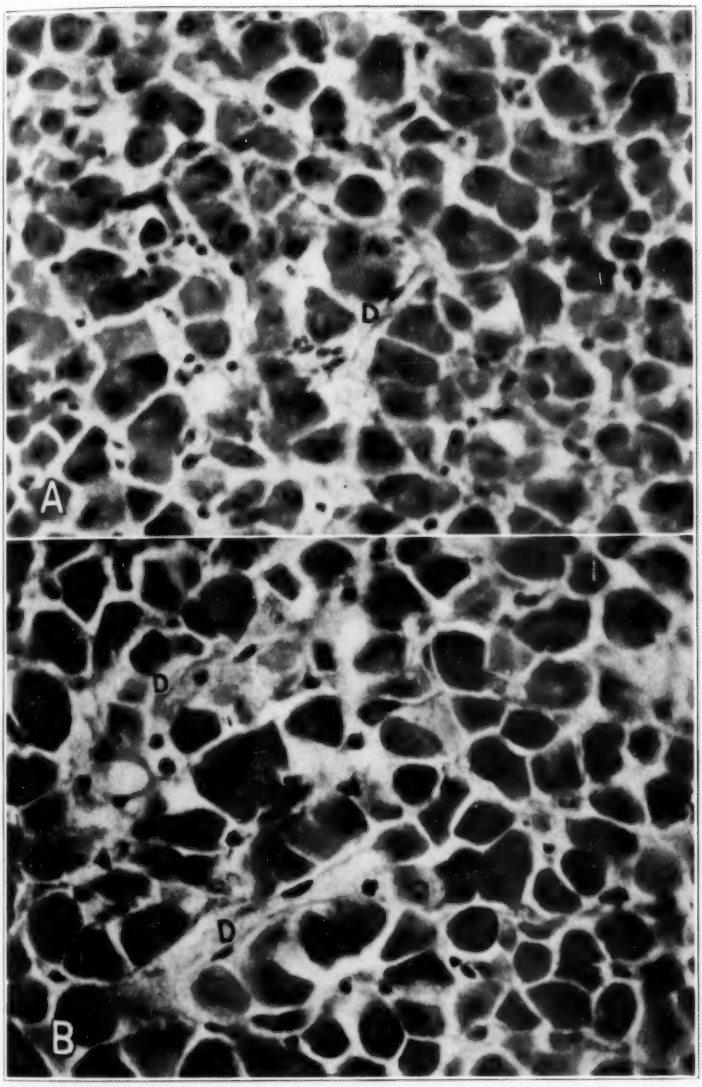


Fig. 2.—Marked dissociation of liver cells. Note the rounding of the borders of the cells and the widening of the Disse spaces (*D*). The nuclei for the most part are intact. In *A* the process is more severe than in *B*.

cells became entirely separated from one another, they became completely round. However, the nuclei were preserved and took the normal stain. The cytoplasm also appeared to be unchanged, as far as the morphologic picture was concerned (fig. 2). The whole phenomenon, which may be described as dissociation, was present in 13 cases and was marked in 7. The changes were not localized and appeared uniformly diffuse.

Furthermore, there was separation of the cords of liver cells as a unit and the walls of the blood capillaries. This space, described by Disse, was thus widened and contained granular masses which stained with eosin. By use of the fluorescence microscope, one of us (H. P.) has shown that the granular masses were plasma proteins and were also found between isolated groups of liver cells. The picture corresponded with that of toxic edema of the liver, or so-called serous hepatitis. It was present in 11 cases and was marked in 7.

Another significant observation was the changes in the liver cells about the central veins, such as shrinking of the cell with pyknosis and granular alterations of the cytoplasm. The latter contained deposits of bile pigment. Sometimes the cells were absent and replaced by granular debris, and the framework was collapsed. This process indicated transition from atrophy of the cells to necrobiosis and necrosis, usually referred to as central necrosis (fig. 3). This was seen in 8 cases, in different degrees, while in 1 case the necrosis was peripheral.

Such degenerative changes as cloudy swelling or fatty degeneration were frequently noted. Fatty changes were observed in the liver in 10 cases; in 4 it was marked. The fatty infiltration was found to be chiefly central in 5 cases and peripheral in 1 and was diffusely distributed in 4.

Bile pigment in the liver cells was localized chiefly centrally (in 12 of 13 cases). In 8 cases it was marked; in 4 it was slight, while in 1 there was only a trace.

The Kupffer cells usually contained bile pigment; in 8 cases they were swollen. The Kupffer cells often assumed a tack shape, since they were slightly displaced but still connected with the cords of liver cells. This picture has been called capillary mobilization by Rössle.[11]

The bile capillaries were dilated and the ramifications marked. In many places there was rupture of the bile capillaries, characterized by a funnel-shaped communication between the lumen of the bile capillary

11. Rössle, R.: Entzündungen der Leber, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1930, vol. 5, pt. 1, p. 250.

and the pericapillary tissue (Disse) space. The wide opening of the funnel was directed toward the Disse space. The ruptures were especially prominent in the center of the lobules, whereas the dilatation was most marked in the periphery.

The bile ducts revealed mostly a narrowed lumen, probably due to compression by edematous periportal tissue. In only 1 case, in which

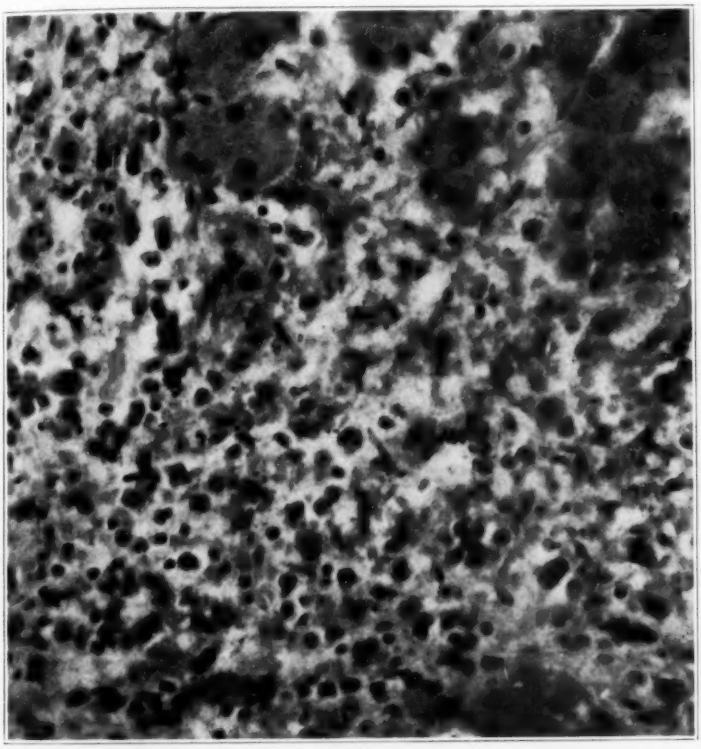


Fig. 3.—Intact swollen liver cells surrounding an area of central necrosis (high power).

there was a clinical history of two months' duration, were the ducts proliferated.

Infiltrations of the periportal septums in the form of round cells was marked in 4 cases, and slight in 7. In 4 cases the septums, in addition to the round cells, showed infiltration of polymorphonuclear leukocytes.

The reticulum fiber framework was usually intact, despite the marked dissociation of the cords of liver cells (fig. 4 *A*). A striking picture was the widening of the network extending between the cords of liver cells

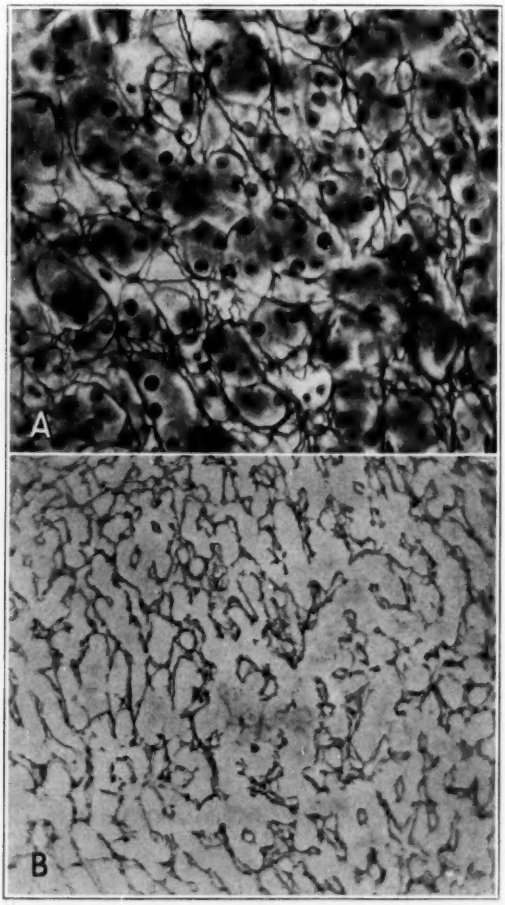


Fig. 4.—Sections specially stained to show reticulum. *A*, reticulum fibers intact in spite of dissociation; *B*, interruption of fibers in the central area.

and the blood capillaries, which indicated dilatation of the Disse spaces due to the edema. In some places, however, actual rupture of the framework was visible about the hepatic veins (fig. 4 *B*).

The spleen was studied in 10 cases. In 4 there was increased fibrosis and in 7 marked congestion, in 6 of which there were focal aggregations of red blood cells, simulating hemorrhages.

The kidneys in 11 cases showed evidences of albuminuria; in 10 there were bile casts in the tubules and in 4 interstitial nephritis. Fatty degeneration and cloudy swelling of the tubules were characteristic; in 3 the changes were marked, while in 7 they were moderate. Proliferation of the glomerular endothelium was observed in 2 cases.

COMMENT

The condition in the cases described represents morphologically a type of fatal parenchymatous jaundice. In many of the cases the clinician had suggested the diagnosis of acute hepatitis. The onset of the disease with jaundice, progressive until death, indicates a primary disease of the liver. Striking is the acute fulminating course, although 2 patients lived longer than a month—two and three months, respectively —from the onset of the illness, but no signs of healing were observed histologically.

The clinical course suggested the diagnosis of acute yellow atrophy of the liver, with an infectious toxic cause, as indicated by fever, chills, pains in the joints and leukocytosis (up to 38,000 per cubic millimeter). A striking feature of differentiation, however, was the enlargement of the liver, which was even noted clinically and was the most prominent anatomic observation. In this respect one may compare our cases with the cases of nonfatal catarrhal jaundice in which the liver is also enlarged. In view of the clinical and anatomic observations, the condition in our cases may therefore be considered as an intermediary stage between catarrhal jaundice and acute atrophy of the liver.

This condition demonstrates that in fulminating parenchymatous jaundice the prognosis may be poor despite an enlarged liver. The study of our cases not only is interesting from a clinical point of view, but may throw light on the still questionable morphologic picture of the enlarged liver in parenchymatous or catarrhal jaundice.

Two different processes were in the foreground. One was damage of the liver cells, characterized by central necroses and heavy infiltration with fat and bile pigment. The presence of bile pigment in liver cells can be considered as a sign of damage since normal liver cells repel the bile pigment immediately and only necrobiotic cells store it. Generalized damage to the liver cells may lead finally to acute atrophy; however, it does not explain the enlargement of the organ, for the liver cells do not increase in size or number.

The enlargement was due to the presence of a protein-rich fluid between the liver cells, or edema. The spaces between the blood capil-

laries and the cords of liver cells, the Disse spaces, were markedly widened and contained coagulated proteins. The presence of proteins indicated that the edema was due to capillary damage, with subsequent inability to retain the plasma proteins within the lumen of the capillaries. Proteins bind water, and when lymphatic drainage is insufficient to carry away the escaped proteins, edema results. When the amount of escaped proteins is high, the increasing fluid accumulates between the cords of liver cells and finally destroys their structure, leading to the dissociation of the cells. The picture of dissociation may be similar to postmortem changes in bodies examined several days after death. In our cases, however, examination was made within three to nineteen hours after death, with only 1 exception (three days). There was no obvious relation between the severity of the histologic changes and the interval between death and autopsy. Marked dissociation was present in a case in which examination was made three hours after death, while it was absent in another in which autopsy was done nineteen hours after death.

The degree of dissociation varied. The interruption of the cords of liver cells was evidently effected not by changes of the cells themselves but by extracellular processes, as indicated by the normal staining of the nuclei. The dissociation and the break-up in some cases was so far advanced that single segregated liver cells were washed away into the blood stream and could be seen within the lumen of the hepatic veins and even in the portal veins (fig. 5). This observation, however, may be considered as insignificant, since it has been seen in other conditions. The same surprising picture was described in cases of acute allylformiate intoxication,[3] the course of which showed the development from the toxic edema to the parenchymatous hepatitis. The framework need not be affected in the presence of dissociation, as shown by special stains (fig. 4). One is, therefore, dealing with damage both to the cells and to the capillaries, in the form of serous hepatitis. The presence of edema fluid rich in proteins between the capillaries and the parenchyma cells causes undernutrition and suffocation of the cells, since the diffusion of metabolic substances and oxygen from the capillaries to the cells is impaired. The cellular damage is responsible for the atrophy of the organ, while the capillary damage explains the enlargement of the liver.

As to the etiologic factor, we are unable to make a positive statement, but a toxin may be assumed. Sometimes a food poison was mentioned in the history, with gastrointestinal symptoms at the onset of the illness. Interesting is the history of the child in our group. Three other children of the same family also acquired jaundice at the same time that the patient was admitted to the hospital, but they recovered, while the patient died seven days after the onset of the illness. From the blood and feces

paratyphoid B bacilli were isolated, and the clinical course did not differ from that seen in the adults of our series. Probably a food poisoning can be suggested as the cause. The children that survived showed a picture similar to what has been described as the epidemic form of catarrhal jaundice.

Fig. 5.—Large numbers of liver cells in the lumen of a large branch of the portal vein in the presence of dissociation.

Other factors, such as syphilis, gonorrhea and infections of the upper respiratory tract, were mentioned in our series. Probably several factors work together in the production of toxic hepatitis, similar to the conditions in catarrhal jaundice.

As to the pathogenesis of icterus, we believe that the combined damage to the capillaries and to liver cells is of importance. Damage

to the liver cells in central necrosis or marked dissociation is responsible for the interruption of the bile capillaries. The break-up of the wall of the capillaries formed by liver cells causes a communication between the bile capillaries and the Disse spaces. Bile escapes into the spaces, which are drained by the lymphatics, and regurgitates through the jugular vein into the general circulation. But in cases in which central necrosis alone is found, no jaundice may be present, as observed in many toxicoses, anemias and even congestion of the liver. On the other hand, simple serous hepatitis alone with widening of the Disse spaces does not cause jaundice. The severest form of serous hepatitis is the condition of the liver in beriberi, and jaundice is not observed with this disease. If merely localized necrosis occurs and the function of the remaining liver cells is intact the regurgitated bile is quickly excreted. However, when the localized central necrosis is combined with diffuse serous hepatitis the excretion of the regurgitated bile is impaired and the bilirubin level of the blood increases. Therefore, a combination of serous hepatitis and damage to the liver cells is the chief factor for the development of the jaundice, and this explanation probably holds for all types of parenchymatous diseases of the liver.

Regeneration of the liver in this condition may be possible in view of the fact that usually the framework of connective tissue is intact and therefore restitution of the cords of liver cells is possible. On the other hand, the existence of this fatal transitional form emphasizes the need for thorough and active therapy in every case of catarrhal jaundice. Therapy directed toward the damaged liver cells is difficult, but the abolishment of the edema may be more easily effected by intravenous injections of hypertonic solution of dextrose. These seem to be of greatest value, since they facilitate dehydration of the interstitial tissues and storage of glycogen.

SUMMARY

Fifteen cases of acute hepatitis are described. The fulminating fatal form appears to be an intermediary stage between catarrhal jaundice and acute yellow atrophy of the liver. The liver in each case was enlarged and characterized morphologically chiefly by damage to the epithelial cells and serous hepatitis, with dissociation of the liver cells. The clinical diagnosis was usually considered as primary hepatitis.

The dissociation of the cords of liver cells may be the result of severe serous hepatitis consequent to damage of the blood capillaries of the liver.

Icterus in parenchymatous jaundice is due to the combination of localized necrosis of the liver cells, or destruction of the cords, and general impairment of the function of the liver cells (serous hepatitis).

The enlargement of the liver in our cases and in cases of catarrhal jaundice is due to toxic edema.

FORMATION OF EDEMA IN THE EYELIDS OF MAN

INFLUENCE OF LOCAL TISSUE PRESSURE, SKIN DISTENSIBILITY, LYMPH FLOW, INTRAORBITAL PRESSURE GRADIENT AND VENOUS PRESSURE

GEORGE E. BURCH, M.D.
NEW ORLEANS

The medical literature is particularly lacking in studies of the formation of edema in the eyelids of man, a subject of much clinical interest, especially in acute hemorrhagic nephritis, in which edema of the eyelids often precedes clinical evidence of edema elsewhere. The reasons for the uneven distribution of edema in this condition have only been conjectured. Fishberg [1] and Landis [2] mentioned the looseness of the tissues of the lids as a possible significant factor responsible, at least in part, for the early presence of edema in that area. They pointed out, however, that other important factors must exist, since in patients with acute hemorrhagic nephritis edema is not likely to develop in other areas of the body where the tissues are loose, such as the abdominal wall of a multipara. Peters [3] stated that "tissue tension, if this is defined loosely as the pressure which resists deformation or distention, must also vary with anatomical structure. This is probably the factor which determines the uneven distribution of edema." Beach,[4] in a discussion of edema of the eyelids, listed many causes of edema in that location, but failed to present any detailed mechanisms for accumulation of the fluid. The current textbooks of ophthalmology have likewise failed to present any adequate discussions of the mechanisms of formation of edema in the eyelids. Loeb,[5] in an extensive review of the literature on edema, included nothing of particular significance concerning edema of the eyelids.

From the Department of Medicine, Tulane University of Louisiana School of Medicine, and the Charity Hospital.

1. Fishberg, A. M.: Hypertension and Nephritis, ed. 3, Philadelphia, Lea & Febiger, 1934, p. 114.

2. Landis, E. M.: Capillary Pressure and Capillary Permeability, Physiol. Rev. **14**:404, 1934.

3. Peters, J. P.: Body Water: The Exchange of Fluids in Man, Springfield, Ill., Charles C. Thomas, Publisher, 1935, p. 52.

4. Beach, S. J.: Edema of the Eyelids, J. A. M. A. **83**:17 (July 5) 1924.

5. Loeb, L.: Edema, Medicine **2**:171, 1923.

This study is an attempt to evaluate some of the factors peculiar to the eyelid that might influence the interchange of fluid between the blood vessels and the tissue spaces within the lid.

METHODS AND MATERIALS

These studies were conducted on 88 living persons, including 57 normal subjects and 31 subjects with various types of edema of the eyelids. The subjects varied in age from 8 to 84 years and included males and females of both the white and the Negro race.

TABLE 1.—*Tissue Pressure in Millimeters of Water for the Eyelids in 15 Normal Subjects* *

Case No.	Age	Sex	Race†	Right Lower Lid			Left Lower Lid		
				Eyes Open		Eyes Loosely Closed	Eyes Open		Eyes Loosely Closed
				Supine	Sitting	Supine	Supine	Sitting	Supine
1	17	M	N	30	32	24	..	..	..
2	59	F	N	24	28	..	..	..	..
3	29	M	W	20	..	..	30	28	28
4	18	M	W	..	..	..	30	32	40
5	27	F	N	20	18	18	..	..	..
6	18	M	N	32	30	32	..	..	..
7	31	M	W	32	38	40	..	..	..
8	28	M	W	20	22	20	..	..	..
9	36	M	W	..	..	..	20	22	22
10	33	M	W	..	..	..	18	20	16
11	64	M	W	30	..	..	28	..	..
12	29	M	W	18	..	..	20	..	..
13	25	M	W	22	..	..	16	..	..
14	27	M	W	20	..	..	21	..	..
15	48	M	W	22	..	..	28	..	..
Mean				24.2	28.0	26.8	23.4	25.5	26.5
Maximum				32	38	40	30	32	40
Minimum				18	18	18	16	20	16

* For the 21 lower lids analyzed collectively, the mean = 23.4 ± 0.7 mm. of water; the standard deviation, 5.1 ± 0.5 mm. of water, and the coefficient of variation, 21.67 ± 2.51 per cent. For the 9 lower lids loosely closed, considered collectively, the mean = 26.6 mm. of water. For the 10 lower lids considered collectively, with the subject in the sitting position, the mean = 27.0 mm. of water.

† In this table and in the accompanying tables, N indicates the Negro and W the white race.

Subcutaneous Tissue Pressure.—With the use of the method previously described,[6] determinations of subcutaneous tissue pressure were made in the lower lids of 15 normal subjects (13 males and 2 females), varying in age from 17 to 59 years. The patients rested quietly in the supine position, and values were obtained with the eyes open and closed loosely as in sleep. The subjects then assumed the sitting position, and determinations were again made with the eyes open. The number of determinations for each lid can be seen in table 1. In 2 normal female subjects, 35 and 50 years of age, the tissue pressure was determined in the evening before they retired and in the morning on awakening. All subjects were instructed not to move the eyeballs and lids during the determinations.

6. Burch, G. E., and Sodeman, W. A.: The Estimation of the Subcutaneous Tissue Pressure by a Direct Method, J. Clin. Investigation **16**:845, 1937.

The effect of the amount of interstitial fluid on subcutaneous tissue pressure was studied in 25 subjects, varying from 17 to 60 years of age. This effect was studied as follows: The adapter, manometer and pressure control unit of the tissue pressure apparatus were connected with one female portion of a three way stopcock, a 1.0 cc. tuberculin syringe was connected with the other female portion and the tissue pressure needle to the third, or male, portion. Sterile physiologic solution of sodium chloride was drawn into the three way stopcock, and the valve was so manipulated that the solution filled the syringe and ran halfway up the adapter. Particular care was taken to remove all bubbles of air from the system. With the subject relaxed in the supine position, the needle was then inserted into the tissues to be studied and the valve of the three way stopcock so adjusted that the tissue pressure could be determined in the usual manner. The valve was readjusted, and 0.1 cc. of the solution of sodium chloride was injected into the subcutaneous tissues. After the valve was reset another measurement of tissue pressure was made. This process was repeated after each 0.1 cc. of solution was injected until the entire 1.0 cc. had been expelled into the subcutaneous tissues. Observations were carried out for the lower lid, the face (area on the level with and about 2.5 cm. anterior to the tragus of the ear), the volar surface of the forearm, the pretibial area, the prepuce of the males and the loose abdominal wall and the breasts of the nonpregnant multiparas. In the first 10 subjects as many of these areas were studied as the sex would permit. Additional subjects were studied until a sufficient number of observations for each area were obtained for analysis. Since the face was not studied simultaneously with the other areas and since the subjects previously used were not available, 7 different subjects were employed for the observations on the face.

Measurements of subcutaneous tissue pressure were made in edematous eyelids of 31 patients, the edema being due to various states (congestive heart failure, 8 patients; acute hemorrhagic nephritis, 2; mediastinal obstruction, 3; low amount of serum proteins, 2; myxedema, 1; infection, 1; senile changes, 10; undetermined cause, 4). All patients were in the supine position when the measurements were made. Repeated determinations were obtained on some subjects during the course of the edema.

Skin Distensibility.—Determinations of skin distensibility were obtained by the method previously described.[7] Certain changes in the apparatus were necessary for its application to the eyelid. A smaller caliper was made which offered a force of approximately 20 Gm.; the bakelite cubes were made smaller so that the width of the "strip" of skin stretched measured 4 mm., and the brass bar for holding the cubes in place for sealing was modified so that the length of the "strip" was approximately 2 cm. The caliper was calibrated, and its calibration curve (fig. 1) was found to have the formula,

$$\text{distance stretched (mm.)} = -1.25 \text{ force (Gm.)} + 51.2.$$

Determinations of skin distensibility were made on both lower lids and on one forearm of 10 normal subjects, varying from 22 to 53 years of age. These subjects included 9 white (7 male and 2 female) persons and 1 Negro male. In 6 of these subjects both sides of the face (area on the level with and about 2.5 cm. anterior to the tragus of the ear) were also studied. The subjects were deliberately chosen with a view to obtaining on the lower lid a strip of skin 2 cm. long which was not arched, thereby eliminating the possibility of an error on

7. Sodeman, W. A., and Burch, G. E.: A Direct Method for the Estimation of Skin Distensibility with Its Application to the Study of Vascular States, J. Clin. Investigation **17**:785, 1938.

straightening an arched portion of the skin. The persons under observation lay in the supine position with the head resting on the occipital region and the face toward the ceiling. For the determinations on the lower lids, the subjects held the eyes vertically rotated toward the eyebrows. This position of the eyes unfolded the lower eyelid. The bakelite cubes were then sealed with collodion to the skin of the inferior portion of the lids so that the "strip" of skin stretched was approximately 10 to 15 mm. from the margin of the lid and almost parallel with it. During the stretching there was no movement at the margin of the lid. With the same small apparatus the distensibility was determined in the forearm in the manner previously described.[7] Determinations of skin distensibility were also made in the lower lids of patients with edema in that region.

Linear Rate of Lymph Flow in the Superficial Lymphatics of the Skin.—The linear rate of lymph flow in the superficial lymphatics of the skin was determined by the method of McMaster.[8] In order that the volume of dye injected intra-

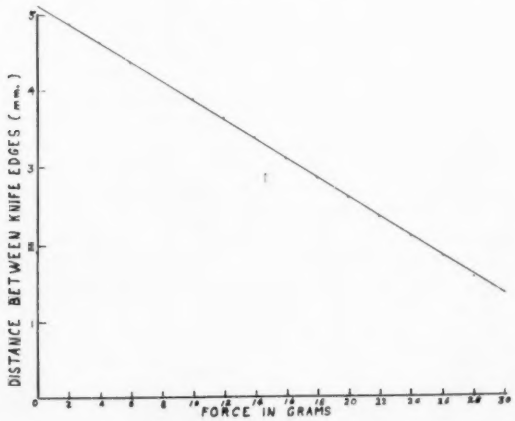


Fig. 1.—Calibration curve for the caliper used in determining the skin distensibility of the eyelid. The formula for the curve is: Distance stretched (mm.) = — 1.25 Force (Gm.) + 51.2.

dermally might be constant and accurate, a specially constructed apparatus, which has been described elsewhere,[9] was employed for the injections. These observations were conducted on the lower eyelids of 9 normal subjects and of 1 subject with mild "senile edema"[10] of the lower lids. All subjects were white men whose ages varied from 22 to 42 years. Eight subjects rested for fifteen minutes in the supine position and one lower lid of each patient was studied.

8. McMaster, P. D.: Changes in the Cutaneous Lymphatics of Human Beings and in the Lymph Flow Under Normal and Pathological Conditions, J. Exper. Med. **65**:347, 1937.

9. Burch, G. E.: A Simple Method for Accurate Injection of Small Volumes of Fluid, Proc. Soc. Exper. Biol. & Med. **40**:676, 1939.

10. The term "senile edema" as employed in this discussion refers to that type of puffiness of the lower eyelids which appears and progresses with senility.

The subjects then assumed the sitting position and the other lid was studied. The other 2 subjects rested for fifteen minutes in the sitting position and one lid of each was studied; they then assumed the supine position for study of the other lid. The temperature and relative humidity were constant (temperature, 75 F.; relative humidity, 50 per cent) during these and all subsequent studies of the lymphatics. The lymphatics were observed as follows: Two hundredths of a cubic centimeter of patent blue V was injected intradermally, as described by McMaster, in the midline of the lid about 5 to 10 mm. from the margin. Tracings of the visible lymphatics were made for record on sheets of cellulose acetate three, ten, twenty and thirty minutes after the injection. The tracings thus obtained were then analyzed in an effort to learn whether or not the upright and supine positions influenced the linear rate of lymph flow.

The effect of blinking on the linear rate of lymph flow in the superficial lymphatics was studied in the upper and lower eyelids of 11 subjects (9 normal persons and 2 with mild senile edema of the lower lids) whose ages varied from 23 to 74 years. The subjects remained seated, and the dye was injected in both lids of one eye, as previously described. After the injection blinking was restricted to a minimum and tracings of the superficial lymphatic vessels were made three, ten, twenty and thirty minutes after the injection. The other eye was similarly studied except that after the injection of the dye blinking was exaggerated. The tracings were analyzed in an attempt to learn whether or not blinking affected the linear rate of lymph flow.

Venous Pressure.—Direct determinations of venous pressure were made in a vein of the lower lid of 2 white male subjects who were 65 and 74 years of age. Both subjects had mild senile edema of the lower lids. Values were obtained for the sitting and the supine position. The technic employed was that previously described,[11] except that an ordinary 27 gage needle without lateral openings was used. Only 2 subjects could be found who did not have an abnormal increase in venous pressure and who, at the same time, had sufficiently prominent and large veins in the lids to permit a direct determination of venous pressure with the use of a 27 gage needle.

Effect on the Volume of the Anterior Orbital Tissue of the Eye of Injections of Sterile Physiologic Solution of Sodium Chloride Into the Posterior Orbital Space in Dogs.—Two dogs were anesthetized with ether after the area around both eyes had been shaved. Capsules of cellulose acetate similar to the capsule employed by Hooker[12] for indirect determinations of venous pressure were then sealed over the eyes with collodion, well away from the margin of the lid. A 22 gage spinal needle was then inserted through the top of the capsule, through the conjunctiva just medial to the eyeball and into the posterior orbital space. The point at which the needle penetrated the capsule was sealed with "lubriseal." The capsule was then connected by rubber tubing to a 1.0 cc. pipet held horizontally, in which there was a small bead of xylene. Sterile physiologic solution of sodium chloride was injected very slowly through the spinal needle in amounts of 0.1 cc. into the posterior orbital space until 1.0 cc. had been injected. Resulting changes in volume of the tissues of the eye anteriorly after each injection of 0.1 cc. were determined by movements of the bead of xylene in the pipet.

11. Burch, G. E., and Sodeman, W. A.: A Direct Method for the Determination of Venous Pressure: Relationship of Tissue Pressure to Venous Pressure, J. Clin. Investigation **18**:31, 1939.

12. Hooker, D. R.: Observations on the Venous Blood Pressure in Man, Am. J. Physiol. **35**:73, 1914.

RESULTS

Subcutaneous Tissue Pressure.—The values obtained for subcutaneous tissue pressure in the eyelids of 15 normal subjects are summarized in table 1. The mean values for 12 right and 9 left lower lids with the eyes open and with the subject lying relaxed in the supine position were 24.2 and 23.4 mm. of water, respectively. Since the difference of 0.8 mm. is within the error for the technic employed, the values for the 21 lower lids were analyzed collectively. These pressures varied from 16 to 32 mm. of water, with a mean of 23.4 ± 0.7 mm. and a standard deviation of 5.1 ± 0.5 mm. The coefficient of variation was found to be 21.67 ± 2.51 per cent, a variation comparable to that of the weights of normal human livers.[13] Figure 2 graphically compares the values for tissue pressure of the lower eyelids with those previously reported[6]

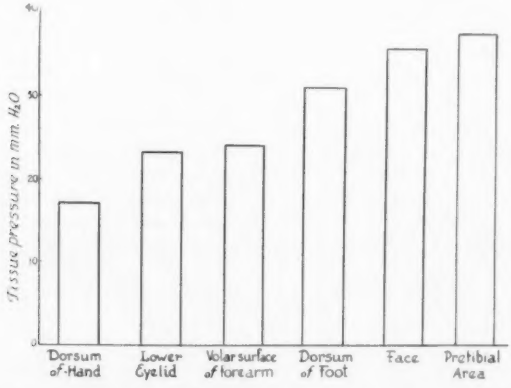


Fig. 2.—Comparison of the mean subcutaneous tissue pressure in the lower lids with that of five other common sites of edema of normal persons.

for the dorsum of the hand, the volar surface of the forearm, the dorsum of the foot and the pretibial area. The mean tissue pressure in 10 normal lower lids, determined with the subject in the sitting position, was 27.0 mm. of water, a difference of 1.4 mm. of water from that determined with the subject in the supine position. When statistical methods were used for the study of small samples[14] this difference was found not to be significant. The mean of the variations of the values for the supine position from those for the sitting position was found to be 1.4 mm. of water, with a standard error of ± 0.95 mm. of water, twice the

13. Pearl, R.: Introduction to Medical Biometry and Statistics, ed. 2, Philadelphia, W. B. Saunders Company, 1930.

14. Mainland, D.: The Treatment of Clinical and Laboratory Data, Edinburgh, Oliver & Boyd, 1938.

standard error being greater than the mean, 1.4 mm. In 9 normal subjects lying relaxed in the supine position with the lids closed loosely as in sleep, the mean subcutaneous tissue pressure was 26.6 mm. of water. By the same method of statistical study the mean of the differences between the values with the eyes closed loosely and those with the eyes

TABLE 2.—*Relation of Tissue Pressure to Increase in Interstitial Volume in the Lower Lid*

Case No.	Age	Sex	Race	Volume of Injected Sterile Physiologic Solution of Sodium Chloride, Cc. 0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
1	17	M	N	30	26	26	24	30	24	23	24	22	24	24
2	59	F	N	24	18	18	18	18	16	10	10	10	10	10
3	29	M	W	30	24	24	22	20	22	24	24	26	30	30
4	18	M	W	40	63	65	60	54	50	52	50	54	50	52
5	22	F	N	20	18	18	30	32	32	32	32	30	30	32
6	18	M	N	32	38	36	34	36	34	36	34	34	30	28
7	31	M	W	32	32	30	30	32	38	44	40	42	43	44
8	28	M	W	20	10	10	12	12	18	20	20	22	20	18
9	36	M	W	20	20	24	24	24	24	24	20	20	18	22
10	33	M	W	18	22	24	30	28	28	30	30	30	32	32
Mean				26.7	27.1	27.5	28.4	28.6	28.6	29.5	28.4	29.0	28.7	29.2
Maximum				40	62	65	60	54	50	52	50	54	50	52
Minimum				18	10	10	12	12	16	10	10	10	10	10

TABLE 3.—*Relation of Tissue Pressure to Increase in Interstitial Volume in the Volar Surface of Forearm*

Case No.	Age	Sex	Race	Volume of Injected Sterile Physiologic Solution of Sodium Chloride, Cc. 0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
1	17	M	N	48	70	100	124	166	192	228	248	152	172	176
2	59	F	N	24	92	88	94	106	108	42	96	102	106	96
3	29	M	W	30	80	130	150	190	200	210	210	208	220	216
4	18	M	W	32	36	40	100	150	154	162	172	184	192	208
5	22	F	N	20	28	68	84	100	122	100	130	131	150	122
6	18	M	N	20	58	104	122	150	158	158	150	190	192	196
7	31	M	W	46	88	124	153	150	168	172	178	178	182	182
8	28	M	W	40	88	100	140	151	184	202	210	222	222	210
9	36	M	W	22	30	38	52	54	58	64	64	100	118	128
10	33	M	W	22	40	52	78	98	112	118	120	122	128	130
Mean				30.4	61.0	84.4	109.7	145.6	145.6	145.6	157.8	158.9	168.2	166.4
Maximum				48	92	130	153	190	200	228	248	222	220	210
Minimum				20	28	38	52	54	58	42	64	100	118	96

open was found to be 1.1 mm. of water, with a standard error of ± 1.7 mm., thus indicating that the values with the eyes open and those with the eyes closed cannot be considered significantly different. In 2 normal subjects the values for tissue pressure in the left lower eyelids during the evening were 16 and 38 mm., and the following morning 18 and 38 mm. of water respectively.

Tables 2 to 8 summarize the effects of the subcutaneous injection of 1.0 cc. of physiologic solution of sodium chloride on the subcutaneous

TABLE 4.—*Relation of Tissue Pressure to Increase in Interstitial Volume in the Prepuce*

Case No.	Age	Race	Volume of Sterile Physiologic Solution of Sodium Chloride Injected, Cc. 0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
1	17	N	36	56	50	50	54	62	54	40	44	40	42
3	29	W	32	40	42	50	60	62	70	70	70	72	74
4	18	W	34	42	52	84	90	110	88	90	90	100	104
6	18	N	40	40	68	68	88	100	88	94	98	104	110
7	31	W	30	34	32	34	36	40	40	42	40	40	40
8	28	W	20	95	104	104	104	110	110	112	114	116	122
9	36	W	18	36	42	44	46	44	44	44	46	48	46
10	33	W	38	48	58	60	62	62	60	62	62	60	62
Mean			31.0	49.0	56.0	61.8	67.5	73.8	69.3	60.3	70.5	72.5	75.0
Maximum			40	95	104	104	104	110	110	112	114	116	110
Minimum			18	34	32	34	46	40	40	40	40	40	42

TABLE 5.—*Relation of Tissue Pressure to Increase in Interstitial Volume in the Pretibial Area*

Case No.	Age	Sex	Race	Volume of Sterile Physiologic Solution of Sodium Chloride Injected, Cc. 0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
2	59	F	N	48	48	84	88	104	112	122	148	166	166	170
3	29	M	W	42	42	120	170	200	226	200	226	250	262	262
4	18	M	W	28	140	144	222	184	218	212	242	264	210	222
5	22	F	N	50	78	108	196	216	232	182	192	206	238	218
6	18	M	N	30	90	144	182	190	204	220	270	290	304	306
7	31	M	W	44	102	164	194	198	206	212	218	221	198	200
8	28	M	W	42	122	200	210	246	130	162	186	204	212	218
9	36	M	W	24	60	82	100	118	128	132	132	140	140	150
10	28	M	W	28	60	84	108	120	126	132	138	144	150	158
Mean				37.3	82.4	125.5	163.3	175.1	175.7	175.0	194.7	209.4	209.0	210.4
Maximum				50	140	200	222	246	232	220	270	290	304	306
Minimum				28	42	82	88	104	112	122	132	144	140	150

TABLE 6.—*Relation of Tissue Pressure to Increase in Interstitial Volume of the Breasts of Multiparas*

Case No.	Age	Race	Volume of Sterile Physiologic Solution of Sodium Chloride Injected, Cc. 0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
2	59	N	16	36	20	40	28	30	32	24	28	28	30
16	26	N	22	30	32	48	58	58	56	64	72	74	74
17	53	N	30	30	52	52	62	64	64	60	60	68	68
18	46	N	32	40	44	44	50	50	50	48	48	48	48
19	60	N	28	46	46	44	46	44	44	40	38	38	39
20	29	N	30	70	76	76	76	80	86	88	88	92	96
21	42	N	32	38	40	46	50	56	62	64	62	64	76
22	39	N	28	42	60	80	84	88	88	92	92	90	92
23	30	N	28	42	52	66	66	68	72	76	82	78	78
Mean			27.3	41.6	46.0	55.1	57.3	59.8	61.6	61.8	63.3	64.4	66.8
Maximum			32	70	76	76	76	88	88	92	92	92	96
Minimum			16	30	20	40	28	30	32	24	28	28	30

tissue pressure in the lower eyelid, volar surface of the forearm, prepuce, pretibial area, breast, abdomen and face of normal subjects. The results for the six areas are graphically illustrated by figure 3. It can be seen that the injection of the physiologic solution of sodium chloride into the subcutaneous tissues of the lower eyelids produced practically no change in the subcutaneous tissue pressure. The mean value of 26.7 mm. of

TABLE 7.—*Relation of Tissue Pressure to Increase in Interstitial Volume of the Abdominal Wall of Multiparas*

Case No.	Age	Race	Volume of Sterile Physiologic Solution of Sodium Chloride Injected, Cc. 0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
5	22	N	18	100	80	82	88	82	58	60	70	78	66
16	26	N	18	20	20	32	44	44	50	54	52	52	58
17	53	N	19	22	40	58	70	70	70	72	74	74	70
18	46	N	16	32	38	68	70	68	68	68	70	78	80
19	60	N	18	28	36	40	40	42	42	40	42	42	38
20	29	N	38	58	110	128	142	110	118	112	104	110	112
21	42	N	44	50	70	72	72	76	80	82	84	90	92
22	39	N	40	42	58	68	70	78	82	84	86	90	92
23	30	N	16	28	38	42	46	44	46	52	54	82	58
Mean			25.2	42.2	54.4	65.6	71.6	68.2	68.2	69.3	70.7	77.3	74.0
Maximum			44	100	110	128	142	110	118	112	104	110	112
Minimum			16	20	20	32	40	42	42	40	42	42	38

TABLE 8.—*Relation of Tissue Pressure to Increase in Interstitial Volume of the Face*

Case No.	Age	Sex	Race	Volume of Sterile Physiologic Solution of Sodium Chloride Injected, Cc. 0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
23	30	F	N	38	108	180	202	214	216	234	242	244	252	256
64	31	F	N	48	70	94	106	106	118	138	146	162	180	184
65	29	F	N	36	100	148	206	160	180	204	246	272	282	306
66	59	F	N	28	70	130	156	197	230	252	272	286	300	320
67	17	F	N	38	68	91	110	136	158	160	178	196	202	208
68	18	F	N	24	112	150	202	206	206	212	214	214	214	228
69	30	F	N	30	110	184	210	262	278	313	333	346	358	366
Mean				35.9	91.1	139.7	170.3	183.0	196.6	216.1	233.0	245.7	255.4	264.0
Maximum				48	112	184	210	262	278	313	333	346	358	366
Minimum				24	68	91	106	106	118	138	146	162	180	184

water increased only to a mean of 29.2 mm. after the injection. The difference between these means was found not to be statistically significant. (Any statistical analysis of data in this paper for samples of less than 15 was performed by the methods previously mentioned,[14] and for those of 15 or greater, by the methods described by Pearl.[13]) There was a definite increase in the values for tissue pressure in the five other areas. This increase was especially marked for the volar surface of the forearm, the face and the pretibial area. In the first site the values rose from a mean of 30.4 mm. of water before the subcutaneous injection

of fluid to a mean of 166.4 mm. of water after the injection; in the face and the pretibial area the rise was even greater, increasing from a mean of 37.3 and 35.9 mm. of water respectively, before the solution of sodium chloride was injected, to 210.4 and 264.0 mm. after the injection. The rises in the tissue pressure produced by the cubic centimeter of solution of sodium chloride injected into the subcutaneous tissues of the breast, the abdominal wall and the prepuce were found to be statistically significant. In these three areas the elevations in the tissue pres-

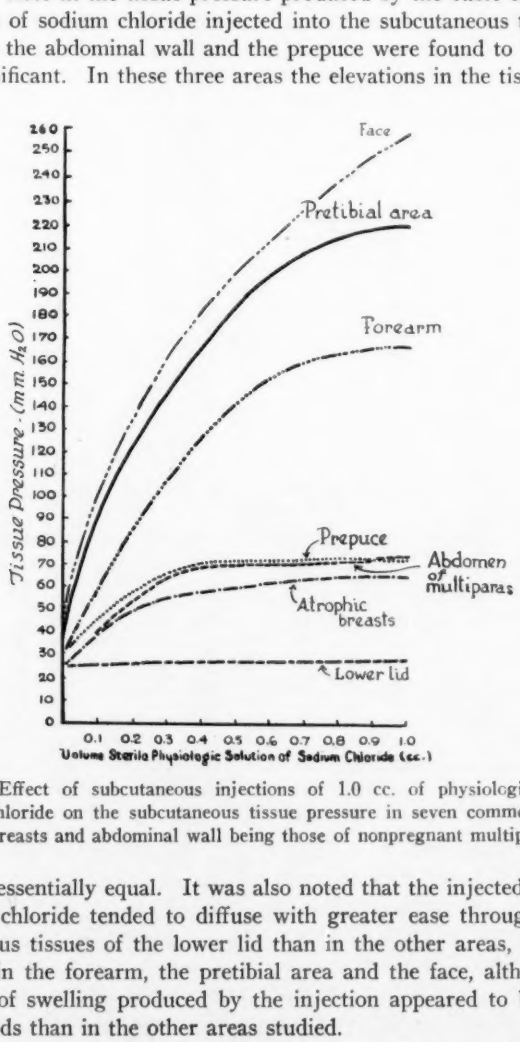


Fig. 3.—Effect of subcutaneous injections of 1.0 cc. of physiologic solution of sodium chloride on the subcutaneous tissue pressure in seven common sites of edema, the breasts and abdominal wall being those of nonpregnant multiparas.

sure were essentially equal. It was also noted that the injected solution of sodium chloride tended to diffuse with greater ease throughout the subcutaneous tissues of the lower lid than in the other areas, and with least ease in the forearm, the pretibial area and the face, although the local area of swelling produced by the injection appeared to be larger in the eyelids than in the other areas studied.

The values for subcutaneous tissue pressure in the patients with edema of the eyelids are summarized in table 9. It can be seen that

TABLE 9.—*Tissue Pressure Values, in Millimeters of Water, for 31 Patients with Edema of the Eyelids and Other Areas*

Case No.	Cause of Edema	Age	Sex	Race	Right Lower Lid	Left Lower Lid	Upper Lid as Indicated	Other Areas as Indicated	Comment
24	Undetermined	52	F	W	36	36	.....	.....	Edema of one year's duration
25	Congestive heart failure	36	M	N	44	..	.....	Prepuce 138	Edema of lid mild; edema of prepuce marked
26	Undetermined	43	F	N	40	42	.....	.....	Moderate amount of edema
27	Myxedema	26	F	W	24	62	.....	.....	9/28/34: Moderate amount of swelling
					44	40	.....	.....	11/4/38: Decreasing edema
28	Mediastinal obstruction	52	F	N	48	58	Right 46 Left 42	.....	Edema marked on right side, moderate on left
29	Exophthalmic goiter	29	F	N	44	48	.....	.....	Cause of edema ?
30	Senility	74	M	W	40	40	.....	.....	Moderate edema
31	Senility	65	M	W	32	42	.....	.....	Moderate edema
32	Malaria and hypoproteinemia	14	M	W	40	..	.....	Right forearm 44	9/1/38: Marked edema of lid; clinically, no edema of arm
					40	..	.....	.....	9/9/38: No edema
33	Senility	70	M	N	..	40	.....	.....	Mild edema
34	Congestive heart failure	37	M	N	..	..	.....	Prepuce 88	Marked edema; no edema of lids
35	Syphilis of central nervous system	38	M	N	32	..	.....	.....	Cause of edema ?
36	Congestive heart failure	55	M	N	28	..	Right 32	Pretibial 60	Relatively much more edema of lids
37	Congestive heart failure	84	M	N	38	..	.....	Pretibial 84	Edema in both areas
38	Infection	40	M	N	..	38	Right 38 Left 40	.....	Left lid was affected and edematous; right lid unaffected
39	Senile changes (?)	38	M	W	48	..	.....	.....	Mild senile type of edema
40	Senility	70	M	W	28	28	.....	.....	Marked edema in left lid, mild in right
41	Mediastinal obstruction	59	F	N	42	38	Right 36 Left 42	.....	Moderate edema of both lids on right side and little in lower left lid
42	Congestive heart failure and chronic hemorrhagic nephritis	40	M	N	24	22	.....	.....	Moderate in both lids
43	Senility	63	M	W	30	16	.....	.....	Moderate edema; very loose lids
44	Acute hemorrhagic nephritis	8	M	N	44	44	.....	.....	10/17/38: Mild edema, 4:30 p. m.
					56	44	.....	.....	10/18/38: Marked edema, 9 a. m.
					28	22	.....	.....	10/24/38: No edema
45	Senility	70	M	W	24	26	.....	.....	Moderate edema of both lids
46	Undetermined	12	F	N	78	44	.....	Forearm 42	Marked edema of lids and none of forearm
47	Senility	48	M	W	24	42	.....	.....	Mild edema in right lid and moderate in left lid
48	Senility	64	M	W	20	16	.....	.....	Mild edema; infection also in right lid
49	Senility	51	M	W	16	16	.....	.....	Mild edema
50	Congestive heart failure	40	F	N	34	26	.....	Forearm 20	11/22/38: Mild in right lid; marked in left; none in forearm
					40	36	.....	52	12/6/38: Moderate in right lid; marked in left; mild in forearm
51	Mediastinal obstruction	58	M	W	50	20	.....	.....	Much lymphedema and infection of right lower lid; none of left lid
52	Congestive heart failure	56	F	N	24	24	.....	.....	Moderate amount of edema and very loose lids
53	Hypoproteinemia	20	F	W	58	..	.....	Forearm 71	Moderate amount in lid; none in forearm clinically
70	Acute hemorrhagic nephritis	30	F	N	18	12	.....	Right forearm 30 Left forearm 30	Marked edema of right lid; moderate edema of left; none of forearms

regardless of the cause of the edema the tissue pressure did not increase to high values. In only 4 instances did it surpass 54 mm. of water, the maximum normal value found for the pretibial area, for which values tend to be consistently high. The maximum value found in any of the eyelids with edema was 78 mm.

Skin Distensibility.—The results obtained for the distensibility of the skin of the lower eyelid, face and volar surface of the forearm in the normal subject are shown in table 10. A difference in the distensibility of 0.18 mm. of stretch per centimeter of skin per 20 Gm. of force was found between the right and the left lower lid. The standard error of this difference was ± 0.21, thus showing that the difference for that group

TABLE 10.—*Distensibility in the Lower Eyelids and in the Volar Surface of the Forearm in 10 Normal Subjects (Units of Distensibility Expressed in Millimeters of Stretch Per Centimeter of Skin Per 20 Gm. of Force)**

Case No.	Age	Sex	Race	Right Lid	Left Lid	Right Side of Face	Left Side of Face	Volar Surface of Forearm
54	29	F	W	0.92	1.26	0.88	0.70	0.46
55	22	F	W	0.92	1.36	0.90	0.84	0.52
56	40	M	W	1.38	1.02	0.62	0.76	0.32
57	37	M	W	0.80	0.84	0.62	0.64	0.36
58	27	M	N	1.64	1.38	0.81	1.02	0.38
59	28	M	W	0.60	0.56	....	....	0.28
60	36	M	W	1.44	1.06	....	....	0.86
61	48	M	W	2.18	1.34	....	....	0.54
62	50	M	W	0.98	1.06	....	....	0.42
63	53	M	W	2.26	1.46	0.40	0.24	0.62
Mean				1.31	1.13	0.71	0.70	0.48
Maximum				2.26	1.46	0.90	1.02	0.86
Minimum				0.60	0.56	0.40	0.24	0.28

* For the 20 lids analyzed collectively, the mean distensibility = 1.23 ± 0.06 mm.: the standard deviation, 0.43 ± 0.04 mm., and the coefficient of variation, 34.73 ± 4.01 per cent.

was not significant. Therefore, the data for the 20 lower eyelids of the 10 normal subjects were analyzed collectively. The mean for the 20 lids was 1.23 ± 0.06 mm. of stretch per centimeter of skin per 20 gm. of force, with the minimum and maximum values 0.56 and 2.26 mm., respectively. The standard deviation was 0.43 ± 0.05 mm. and the coefficient of variation 34.73 ± 4.01 per cent. It can be seen from the table that the skin of the lower lid is approximately two and a half times as distensible as that of the volar surface of the forearm and twice that of the face. It was previously found [7] that the distensibility of the skin of the volar surface of the forearm was about three times that of the pretibial area, twice that of the dorsum of the foot, three-fourths that of the dorsum of the hand, and one-half that of the abdomen. These results indicate quantitatively that the distensibility of the skin of the lower eyelid is greater than that of the other regions mentioned, being

closely approached only by that of the skin of the abdomen. This relative difference is graphically illustrated by figure 4, in which the distensibility of the skin of the forearm was arbitrarily expressed as 100. Obviously, actual values could not be graphed, since the width and length of skin, as well as force, used in these studies on the eyelid differed from those used in previously reported studies on the pretibial area, the dorsum of the hand and foot and the abdomen. However, since the skin of the forearm was studied under both conditions, it was used as the standard for reference in the construction of the figure.

Linear Rate of Lymph Flow in the Superficial Lymphatics.—In the 10 white male subjects studied by the McMaster method, the linear rate of lymph flow in the lower eyelid was invariably more rapid in the

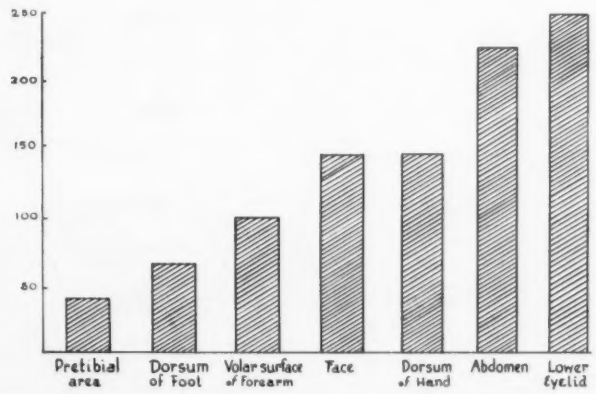


Fig. 4.—Comparison of the values for skin distensibility of seven areas of the body of normal subjects. The figure was constructed on the basis of the distensibility of the skin of the volar surface of the forearm, which was arbitrarily considered to be 100.

sitting than in the supine position. Tracings from a typical subject are shown in figure 5. Not only was the rate of flow more rapid in comparable vessels in the sitting than in the supine position but, in many instances, there was an increase in the number of vessels filled. These findings are in agreement with those of McMaster, who observed similar positional effects on the lymph flow in the superficial lymphatics of the forearm. It was also noted that the rate of diffusion of the dye in the original wheal at the site of injection in some instances tended to be more rapid in the skin and subcutaneous tissues of the lid than that described for the forearm by McMaster. This difference was also noted in the forearms of subsequent subjects studied during other observations. In the 2 subjects with senile edema of the lower lids the linear rate of

lymph flow was also greater with the subject in the sitting than in the supine position. The results of studies on the 2 subjects in whom the observations were made first in the sitting and then in the supine position did not differ discernibly from those on the other 8 subjects in whom the order of observation was reversed.

In the 11 white male subjects (9 normal and 2 with senile edema of the lower eyelids) it was found that, except in the upper eyelids of the 2 normal subjects, the linear rate of lymph flow was much more rapid with blinking of the lids. This is illustrated by a typical case shown in figure 6. These results are in agreement with those of McMaster, who found that exercise increased the linear rate of lymph flow in the superficial lymphatics of the forearm. In the 2 exceptions there was no appar-

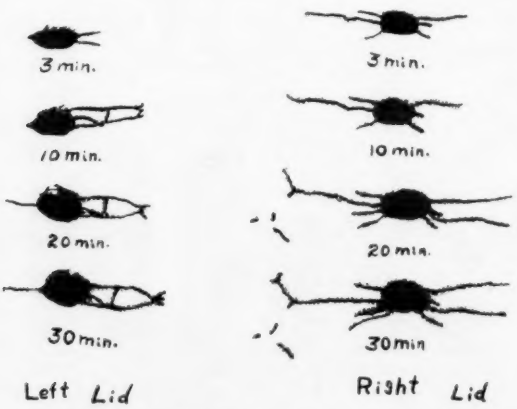


Fig. 5.—Effect of position of the subject on the linear rate of lymph flow in the superficial lymphatics in the lower eyelids of a typical subject, the tracings of the lymphatics being made three, ten, twenty and thirty minutes after the intradermal injection of patent blue V. Observations on the left lid were made with the subject in the supine position and those on the right with the subject sitting. The vessels draining nasally are to the left.

ent difference in the rate of flow in the upper lids with and without the influence of blinking; in the other subjects the temporal direction of flow was more rapid with blinking, while the nasal direction of flow was more rapid without blinking. A satisfactory explanation for these differences cannot be advanced at present. They may be due to the fact that the drainage was into the deeper tier of lymphatics, which anastomose with the superficial lymphatics,[15] thereby precluding the observation of the

15. Most, A.: Ueber die Lymphgefässe und die regionären Lymphdrüsen der Bindehaut und der Lider des Auges, Arch. f. Anat. u. Physiol., 1905, pp. 96-110.

flow. Blinking produced more rapid diffusion of the dye from the lymph vessels as well as more rapid spread of the dye from the original site of injection. No discernible difference in the results could be found between the 2 subjects with senile edema of the lower lids and the 9 normal subjects.

Venous Pressure.—In the 2 subjects who had veins of the lower lid sufficiently large for direct measurements of venous pressure, the venous pressures were found to be 10.6 and 12.4 cm. of water respectively, in the supine position and 4.8 and 2.2 cm. in the sitting position. Both of these patients suffered from senile edema of the lower eyelids, but were free from any evidence of venous obstruction.

Effect on the Volume of the Anterior Orbital Area of Injecting Physiologic Solution of Sodium Chloride into the Posterior Orbital

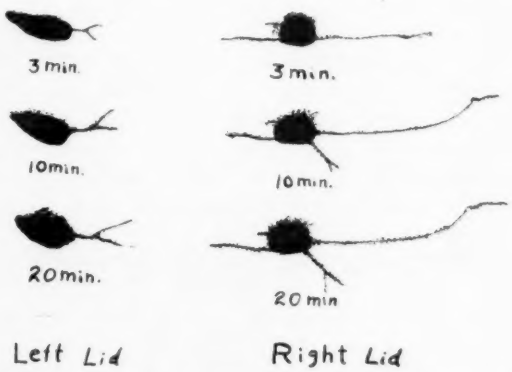


Fig. 6.—Effect of blinking on the linear rate of lymph flow in the superficial lymphatics in the lower eyelids of a typical subject, the tracings being made three, ten and twenty minutes after intradermal injection of patent blue V. Observations on the left lid were made with blinking maintained at a minimum and on the right with blinking exaggerated. The vessels draining nasally are to the left.

Space.—The changes in volume noted for the anterior orbital structures of both eyes of 2 dogs during the injection of 1.0 cc. of physiologic solution of sodium chloride into the posterior orbital space are summarized in figure 7 *A, B, C* and *D*. With the injection of the solution of sodium chloride there was a concomitant change in the volume of the tissues anteriorly; that is, the eyelids, and probably the eyeball, were pushed outward. The lids could be seen to become more prominent. It could not be determined by inspection whether this increase in prominence of the lids was due to deep structures pushing the lids anteriorly or whether there was an actual accumulation of fluid in the lids. There

was a lag, however, between the completion of each injection and the occurrence of the maximum change in volume of the structures anteriorly. This lag will be discussed more fully later.

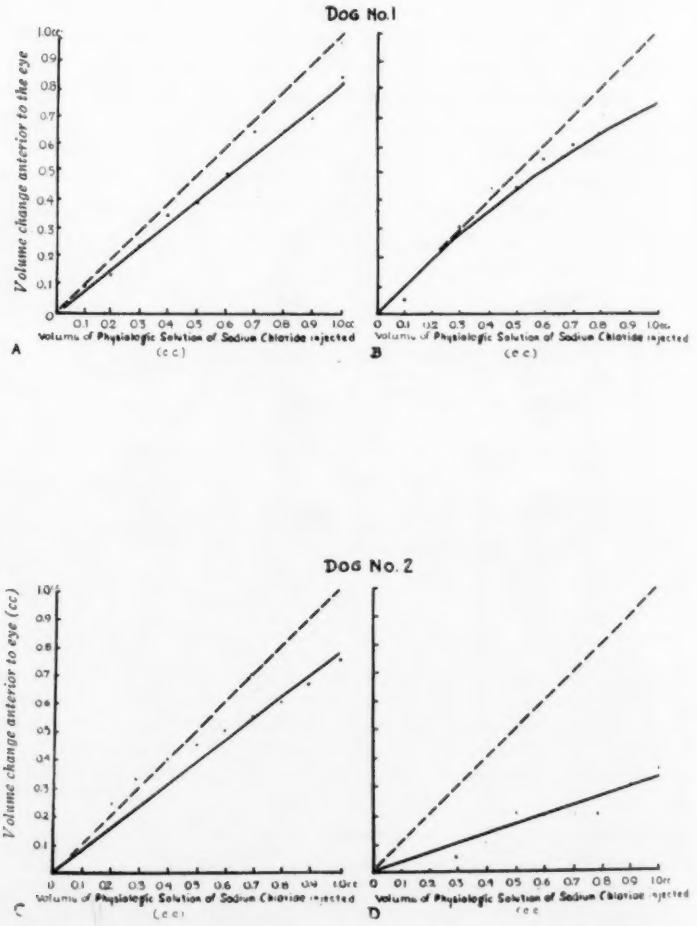


Fig. 7.—Effect of injection of 1.0 cc. of physiologic solution of sodium chloride in the posterior orbital space on the volume of the anterior orbital structures of 2 dogs. *A* and *D* show the results for the left eyes of the respective dogs, and *B* and *C*, for the right eyes. The interrupted line illustrates the curve that would result were the changes in volume of the anterior structures equal to the volume of the solution of sodium chloride injected in the posterior orbital area. The continuous line illustrates the actual results.

COMMENT

A mean subcutaneous tissue pressure for the lower eyelids of 23.4 mm. of water, a value almost equal to the mean pressure of 23.6 mm. previously found [6] for the forearm, would at first prompt one to consider the looseness of the tissues of the eyelids of little significance in facilitating the accumulation of interstitial fluid in the lids. Surely, from these findings alone, it would not seem that tissue tension influenced the volume of interstitial fluid any differently in the eyelids than in the forearm. However, when 1.0 cc. of isotonic solution of sodium chloride was injected into the subcutaneous tissues of the volar surface of the forearm, a relatively great rise in tissue pressure occurred, while a similar injection into the subcutaneous tissues of the lower lid produced almost no change in tissue pressure. An increase of 0.1 cc. in the volume of the local subcutaneous tissue produced a greater rise in subcutaneous tissue pressure in the forearm, as well as in all other areas studied, than a change of volume ten times as great produced in the eyelid. It appears from these findings that the differences in the values for tissue pressure are not due entirely to differences in diffusion of the injected fluid, but in a large part to variations in distensibility of the respective tissues. Furthermore, in the presence of edema, which was marked in some instances, the subcutaneous tissue pressure of the eyelids was found to be relatively little increased regardless of the stage of the edema (table 9). On the other hand, in some instances, tissue pressure was found to rise markedly in the forearm in the presence of relatively less, but progressing, edema. Subjects 9 and 30 (table 9), who were suffering from hypoproteinemia, a condition tending to produce edema with equal force throughout the body, had edema of the eyelids and not of the forearm. At the same time, in both subjects the subcutaneous tissue pressure in the eyelids, in spite of the local edema, was less than that in the nonedematous forearm. Essentially the same sort of relationship as that observed between the eyelid and the forearm was also found in other areas studied, namely, the loose pendulous breasts and loose abdominal wall of multiparas, the prepuce and the pretibial area. In the first three areas the difference was not as marked, but nevertheless it was sufficient to be significant. It has also been noted [16] that in cases of scleroderma, a condition in which the subcutaneous tissues are dense and atrophic, the antithesis to the state of the tissues of the normal eyelids, the tissue pressure is greater than in a similar uninvolved area; likewise, the development of edema produced a marked increase in the tissue pressure. These

16. Sodeman, W. A., and Burch, G. E.: (*a*) The Tissue Pressure in Subcutaneous Edema, Am. J. M. Sc. **194**:846, 1937; (*b*) Tissue Pressure: An Objective Method of Following Skin Changes in Scleroderma, Am. Heart J. **17**: 21, 1939.

data tend to indicate that the looseness of the tissues of the eyelids renders them distensible, so much so that they are unable to benefit much from the limiting influence of tissue pressure on the formation of edema. It is probable, however, that with very marked edema and considerable distention of the lids, tissue pressure may become a significant factor in limiting the formation of edema. Therefore, on the basis of tissue pressure alone, in the presence of any state that would tend to favor an equal accumulation of tissue fluid throughout the body, the eyelids would be less capable of preventing or limiting the accumulation of fluid and would be expected to become edematous early. Since tissue pressure in the lids was not found to vary with the position, the time of day or the position of the lids, that is, whether they were open or loosely closed, as in sleep, one would not expect the interstitial fluid of the lids to vary under those circumstances as a result of tissue pressure. This is particularly significant, as will be discussed later, in the explanation of the tendency for edema of the lids to develop during sleep when the subject is in the supine position and to disappear when the patient is up and about.

The studies of distensibility ("stretchability") of the skin of the lower eyelids of normal subjects showed it to be greater than that of any other common site of edema studied, even than that of the abdominal wall. As stated previously,[7] the skin acts as an important factor in limiting tissue pressure and, in turn, edema formation. The extreme distensibility of the skin of the eyelids apparently has relatively little effect on the underlying subcutaneous tissue pressure, at least until large amounts of interstitial fluid have accumulated. This was evidenced by the failure of the tissue pressure to rise when fluid was injected subcutaneously and by the relatively small elevation in patients with edema of the lids. It appears, therefore, that, all things being equal, on the basis of distensibility of the skin, edema would tend to develop more readily in the eyelids than in the pretibial area, the dorsum of the hand and foot, the forearm, the face and probably the abdominal wall. In nonpregnant multiparas the values for distensibility of the skin of the abdominal wall and of the eyelids approximate each other so closely that it is impossible to be certain that distensibility of the skin influences formation of edema any differently in the two areas.

The studies of the linear rate of lymph flow in the superficial lymphatics of the eyelids showed it to be greater with the subject in the upright than in the supine position. This was evidenced by an increase in the linear rate of flow in similar vessels as well as by an increase in the number of vessels visualized, and tends to show that when the effects of gravity favor the return of lymph to the venous circulation the rate of lymph flow is increased. Therefore, during the day, when a person is up and about and performing his daily duties, the drainage of lymph from the lids is more active than it is at night, when he is asleep and resting

horizontally in bed. Although this gravitational effect on lymph flow may not abnormally influence the accumulation of interstitial fluid in the eyelids during sleep, it must facilitate rapid removal of such fluid during the day and must be significant in the presence of edema of the lids.

Since the linear rate of lymph flow in the superficial lymphatics is increased by movement, such as blinking, of the lids, it may be surmised that during sleep, when movement of the lids is at a minimum, lymph flow is not so rapid as during the day, when movement of the lids is relatively great. Sleep would, therefore, favor the accumulation of interstitial fluid, while movement of the lids during the day would favor its removal. On this basis, then, edema of the eyelids would be more likely to disappear during the day, when the person is awake, while during sleep, when the lids are comparatively motionless, the removal of edema fluid by the lymphatics would be less active.

In the 2 subjects in whom there was a superficial vein of the eyelid sufficiently large for direct determination of venous pressure, the venous pressure was found to be lower with the subjects in the sitting than in the supine position. These observations, though limited to only 2 subjects, suggest strongly that the hydrostatic, or filtration, pressure in the capillaries of the eyelids is decreased when a subject assumes an upright position. Landis [17] has shown that elevation of the hand above the level of the heart decreases the hydrostatic, or capillary, blood pressure. There is no reason to doubt the occurrence of a similar effect in the capillaries of the eyelid when a person assumes an upright position and the eyelids are above the level of the heart. Therefore, interstitial fluid would tend to accumulate more rapidly with the subject in the supine than in the upright position because of the variations in venous pressure in the respective positions. On the basis of venous pressure alone, it might be expected that, in a person suffering from a condition tending to produce edema generally, edema would be more likely to develop in the lids at night during sleep and would disappear more readily during the day, when he is upright.

The eyelids are peculiar anatomically in that they enclose anteriorly a pyramidal space, the orbit, containing incompressible material surrounded, except at its anterior surface, or base, by rigid bony walls and relatively incompressible material. In order for any material to accumulate in the orbit, it would have either to displace blood from the adjacent vessels or to push tissue and fluids anteriorly, where the walls are distensible. It is unlikely that only blood would be displaced, and then, if at all, probably to only a minor extent, unless the localized tissue

17. Landis, E. M.: Micro-Injection Studies of Capillary Blood Pressure in Human Skin, Heart **15**:209, 1930.

pressure exceeded the arterial diastolic pressure, a condition which is unlikely in edema. Furthermore, with diffuse moderate compression of blood vessels, intravascular pressure in the compressed vessels, capillaries, venules and small veins would be built up from the arterial side to reestablish blood flow. It has been shown that in edema the tissue pressure is unlikely to increase sufficiently to exceed even capillary blood pressure for any great length of time.[16a] It appears, therefore, on a purely theoretic basis, that edema fluid which accumulates in the posterior orbital space, tending to raise tissue pressure locally, will flow intercellularly into the distensible eyelids, where tissue pressure is and remains relatively low even in the presence of much edema. The studies of Charpy and Clermont [18] tend to support this reasoning. They injected colored gelatin into the posterior orbital spaces of fresh cadavers and noted bulging of the tissues anteriorly, with an occasional rupture of the nasal portion of the orbital septum and escape of the material into the lids. In 1 instance the colored gelatin flowed freely from the posterior orbital space into the lids and filled the subcutaneous tissues. In the orbits injected by these observers, the material did not progress posteriorly, but invariably migrated anteriorly. With rapid injections the orbital septum acted as a barrier to the escape of the material into the eyelids. On the other hand, the authors stated that with a gradual accumulation of interstitial fluid, as in edema, the interstitial fluid would diffuse freely through the orbital septum and lodge in the subcutaneous tissues of the eyelids. Heerfordt [19] obtained essentially the same results in cadavers after the injection of air into the posterior orbital space. The increase in volume noted for the tissues anterior to the orbits of 2 dogs after the injection of physiologic solution of sodium chloride into the posterior orbital spaces (see page 491) lends further support to the idea that interstitial fluid which tends to accumulate in the posterior orbital space probably migrates anteriorly into the subcutaneous tissues of the lids. In the four orbits injected the total change in volume anteriorly was not equal to the total volume of physiologic solution of sodium chloride injected into the posterior region of the orbit. This is probably due in part to displacement of blood and errors in the method employed. The lag in the change in volume anteriorly after the injection of fluid into the orbits is probably due to the reaccumulation of displaced blood and also to seepage of the injected solution into the anterior tissues of the orbit.

18. Charpy and Clermont: Structure topographique des paupières et épanchements intrapalpébraux, Bibliog. anat. **21**:65, 1911.

19. Heerfordt, C. F.: Ueber das Emphysem der Orbita, Arch. f. Ophth. **58**: 123, 1904.

Although the venous pressure and lymph flow of the face are affected by postural changes in essentially the same way as are those of the eyelids, the effects on tissue distensibility are different, as shown by the studies of tissue pressure and skin distensibility. These structures differ further in that the eyelids probably accommodate most of the excessive amount of interstitial fluid that escapes into the intraorbital space as well as that which escapes into the tissue spaces of the eyelids themselves. The tissues of the face, like those of other areas of the body studied, accommodate only the fluid escaping into them. On the basis of these observations, therefore, edema would be expected to develop more readily in the eyelids than in adjacent areas, namely, the face.

It is more than likely that in a disease tending to produce edema generally, such as acute hemorrhagic nephritis, edema fluid accumulating in the intraorbital space migrates into the distensible eyelids, thus making the eyelids swell more than they would if they had to accommodate only the edema fluid accumulating in the lids themselves. This might render the eyelids clinically edematous before other areas of the body in which a similar anatomic peculiarity does not exist. As Drury and Jones [20] have shown, it is necessary for a part to increase approximately 8 per cent in volume before clinical edema is manifested, and since the eyelids probably accommodate interstitial fluid accumulating in the whole orbit as well as in their own tissues, the lids might experience an increase of 8 per cent in volume before other areas which accommodate only the fluid escaping into their own tissues.

SUMMARY

The mean subcutaneous tissue pressure in the lower eyelids of 21 normal subjects was found to be 23.4 ± 0.7 mm. of water, with a standard deviation of 5.1 ± 0.5 mm. The minimum and maximum variations were 16 and 32 mm. of water, respectively. Subcutaneous tissue pressure in the eyelids remained practically the same when 1.0 cc. of a physiologic solution of sodium chloride was injected subcutaneously. There was a definite rise in the subcutaneous tissue pressure when a similar amount of physiologic solution of sodium chloride was injected subcutaneously into the loose, pendulous breasts and loose abdominal wall of a multipara and into the prepuce, and there was a comparatively marked rise when the solution was injected into the subcutaneous tissue of the volar surface of the forearm and the pretibial area. Even with marked edema of the eyelids due to various causes the subcutaneous tissue pressure of the lids increased relatively little.

20. Drury, A. N., and Jones, N. W.: Observations upon the Rate at Which Edema Forms When the Veins of the Human Limbs Are Congested, Heart **14**: 55, 1927.

The skin of 20 lower eyelids was found to be very distensible, having a mean distensibility ("stretchability") of 1.23 ± 0.06 mm. of stretch per centimeter of skin per 20 Gm. of force, with minimum and maximum variations of 0.56 and 2.26 mm., respectively. The standard deviation was 0.43 ± 0.05 mm. The distensibility of the skin of the eyelids was found to be approximately five times that of the pretibial area, four times that of the dorsum of the foot, two and a half times that of the volar surface of the forearm, twice that of the face, one and three-fourths times that of the dorsum of the hand and one and two-tenths that of the abdomen.

The linear rate of lymph flow in the superficial lymphatics of the skin of the eyelids with the subject resting quietly in the supine position was found to be increased by blinking or by the subject's merely assuming the sitting position.

Direct determinations of the venous pressure in the veins of the lower lid of 2 subjects without venous obstruction and with veins sufficiently large for venipuncture showed a marked decrease when the subjects changed from the supine to the sitting position.

The injection of physiologic solution of sodium chloride into the posterior orbital area of dogs increased the volume of the anterior tissues of the orbit. This increase was considered an indication of a probable migration anteriorly of edematous fluid, which escapes to the only freely distensible portion of the rigidly enclosed orbit containing incompressible material.

CONCLUSIONS

These data indicate that in the eyelids of a subject suffering from a condition tending to produce edema equally throughout the body, such as acute hemorrhagic nephritis, edema would develop more readily and probably earlier than in other common sites of edema because of the marked distensibility of the eyelids, the absence of early and marked benefits from the local tissue pressure and restraining skin in limiting formation of edema and the fact that the lids accommodate not only the edema fluid escaping into their own tissues but also that of the whole orbital cavity. The edema would be most apt to develop early during sleep because at that time the lymph flow is most sluggish, movement of the lids and gravitational effects favoring lymph flow are at a minimum and venous pressure is most marked. Conversely, the edema would be expected to disappear during the day, when the patient is up and about.

PEPTIC ULCER AND ACHLORHYDRIA

A FURTHER STUDY OF THE ROLE OF ACID GASTRIC JUICE IN THE PATHOGENESIS OF PEPTIC ULCER

WALTER LINCOLN PALMER, M.D.
AND
PAUL B. NUTTER, M.D.
CHICAGO

The concept that acid gastric juice plays an essential role in the genesis of peptic ulcer is supported by a great deal of clinical, pathologic and experimental evidence. A number of points, however, are not yet clear. Apparently incompatible with this thesis is the alleged occurrence of chronic ulcer with achlorhydria. In this paper we wish to consider the question as to whether or not peptic ulcer occurs in the complete absence of acid gastric juice.

In 1926 one of us (W. L. P.) reviewed the literature on this subject, studied a group of cases and concluded that there was no *conclusive* evidence that chronic ulcer occurs in the complete absence of acid gastric juice.[1] The evidence usually offered to prove that ulcer may occur in the presence of achlorhydria was found inadequate either in demonstrating achlorhydria or in establishing the presence of chronic benign ulcer, or, indeed, in both respects. It was pointed out that before the diagnosis of ulcer with anacidity may be made the anacidity must be "histamine proved" and the ulcer must be shown not only to be present but to be not syphilitic, tuberculous or carcinomatous. In a series of over 1,000 cases of gastric and duodenal ulcer studied at that time, no instance of chronic benign ulcer occurring in the presence of complete achlorhydria was found.

Since then, various authors have reported instances of "ulcer with achlorhydria." Cheney,[2] in 1927, described a case of chronic benign gastric ulcer in which two evening samples of gastric juice failed to show any free acid and the continuous quantitative estimation of

From the Department of Medicine, the University of Chicago.

A brief résumé of this paper was presented before the Association of American Physicians at Atlantic City, N. J., May 2, 1939.

1. Palmer, W. L.: The Mechanism of Pain in Gastric and Duodenal Ulcers: I. Achlorhydria, Arch. Int. Med. **38**:603 (Nov.) 1926.

2. Cheney, G.: Peptic Ulcer and Achlorhydria, California & West. Med. **27**:78, 1927.

gastric secretion by the method of Bloomfield and Keefer [3] showed very low ten minute secretions, rapid emptying time and no acid reaction to Töpfer's reagent or to neutral red in any of the specimens, the total acidity reaching only 6 degrees. At operation an "almost completely healed ulcer measuring 3 by 4 cm." was found. It is significant that no histamine test was carried out and that an Ewald test meal six months earlier had shown free acidity of 26 and total acidity of 39 degrees. Apparently the stomach was able to secrete acid gastric juice at the time the ulcer developed.

Wilson and Earl [4] described a case of gastric ulcer in which repeated Ewald test meals failed to disclose free acid whereas a fractional histamine test revealed a maximum free acidity of 16. "At operation a small, indurated, partially healed ulcer with a shallow crater, 4 mm. in diameter, and a zone of induration of 1.5 cm. diameter was found. . . . The microscopic sections . . . gave no evidence of malignancy." In a second case of gastric ulcer described by these authors the Ewald test meal yielded no free hydrochloric acid, but the histamine test disclosed the maximum of free acidity to be 32 degrees.

Abramson [5] found the evidence demanded by Palmer "too severe" and estimated that the incidence of achlorhydria in cases of gastric ulcer was 13.5 per cent. In a series of 89 cases, he observed 3 in which no free acid was found by fractional analysis after a rusk test meal (a modified Ewald) or after histamine given simultaneously with a rusk test meal. Two of these 3 cases were so-called recent cases. Further details were not given. These cases may indeed have been instances of chronic ulcer with complete and persistent achlorhydria, but the report is too brief to be completely convincing. Miller, Prendergrass and Andrews,[6] in a study of 30 cases of gastric ulcer, found 1 instance of achlorhydria; but here also the evidence for the diagnosis was based on a single Ewald test meal and was therefore insufficient. The case of active duodenal ulcer described by Braimbridge [7] was adequately proved so far as the presence of active ulcer was concerned,

3. Bloomfield, A. L., and Keefer, C. S.: A Method for the Continuous Quantitative Estimation of Gastric Secretion and Discharge in Man, Arch. Int. Med. **37**:819 (June) 1926.

4. Wilson, J. A., and Earl, G.: Achlorhydria and Hypochlorhydria in Peptic Ulcer, Minnesota Med. **15**:79, 1932.

5. Abramson, L.: Occurrence of Achlorhydria in Gastric and Duodenal Ulcer, Acta med. Scandinav. **77**:77, 1931.

6. Miller, T. G.; Prendergrass, E. P., and Andrews, K. S.: A Statistical Study of Clinical and Laboratory Findings in Gastric and Duodenal Ulcer, Am. J. M. Sc. **177**:15, 1929.

7. Braimbridge, C. V.: An Unusual Case of Duodenal Ulcer, East African M. J. **14**:172, 1937.

but the diagnosis of achlorhydria rested on a single fractional test meal (type not stated). Moutier and Colmenares [8] stated that one of them had encountered 2 cases of gastric ulcer with achlorhydria, but they gave no details. Vanzant, Berkson, Alvarez and Eusterman,[9] after reviewing the literature, concluded that achlorhydria "is present just as often in patients with ulcer of the stomach as in normal persons." If this is true, the incidence of anacidity, as demonstrated by the histamine test, in patients with chronic gastric ulcer should be over 10 per cent, for Bloomfield and Polland [10] found the incidence in normal persons to be 11.9 per cent. We have not been able to find satisfactory evidence of such an incidence in patients with chronic gastric ulcer.

Fig. 1.—Maximum free acidity of gastric contents recorded after various tests in 84 cases of gastric ulcer.

Gutzeit [11] described an acute ulcer seen gastroscopically in the stomach of a patient with pernicious anemia and histamine-proved

8. Moutier, F., and Colmenares, J.: Ulcère duodénal avec achlorhydrie chez un syphilitique, Arch. d. mal. de l'app. digestif **27**:980, 1937.

9. Vanzant, F. R.; Berkson, J.; Alvarez, W. C., and Eusterman, G. B.: Changes in Gastric Acidity Associated with Peptic Ulcer, Cholecystitis, and Other Diseases, Analyzed with the Help of a New and Accurate Technique, Arch. Int. Med. **52**:616 (Oct.) 1933.

10. Bloomfield, A. L., and Polland, W. S.: Gastric Anacidity, New York, The Macmillan Company, 1933, p. 53.

11. Gutzeit, K.: Die Gastroskopie im Rahmen der klinischen Magendiagnostik, Berlin, Julius Springer, 1929.

achlorhydria. Symptoms of ulcer were not present. The accidental observation was not confirmed by further gastroscopic or roentgen examinations.

Our own observations on acidity in cases of gastric ulcer in the past eleven years are summarized in the scatter diagram of figure 1. In 84 cases of chronic gastric ulcer no instance of complete and persistent achlorhydria was found. In 1 instance the single gastric analysis made was carried out after an Ewald test meal and showed free acidity

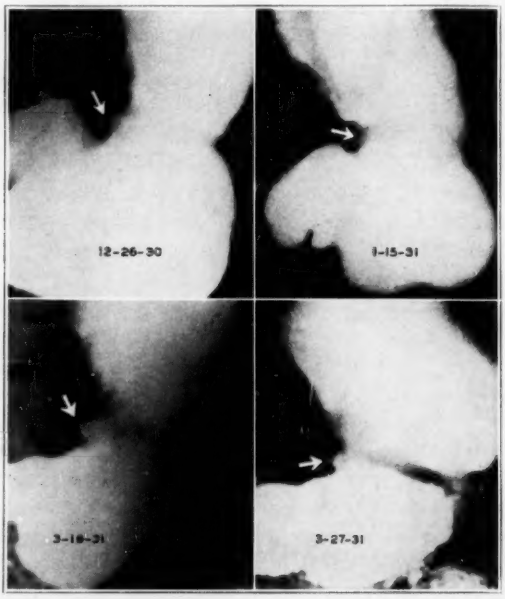


Fig. 2 (case 1).—Small chronic gastric ulcer, with moderate hourglass deformity, associated with low gastric acidity (maximum free acidity after histamine, 18 degrees).

of only 4. A histamine test was not done. It would almost surely have shown higher values.

Three cases of our series are of such interest as to warrant rather detailed descriptions.

REPORT OF CASES

CASE 1.—A woman 51 years of age was admitted to the hospital Dec. 11, 1930, because of abdominal distress, which conformed to the ulcer pattern, of two years' duration. The pain had first appeared six years prior to her admission and had lasted until the patient was operated on two years after the onset. The surgeon at that time found "an old healed peptic ulcer with marked cicatricial contraction"

and hourglass formation between the middle and lower thirds of the stomach; the scar was excised. Ewald test meals at that time were reported to have disclosed free acidity of only 10 and 12 degrees. The patient remained well for two years and then the distress recurred. At the time of admission to the hospital in 1930, roentgen examination disclosed a penetrating ulcer of the lesser curvature, with moderate hourglass formation (fig. 2). The patient was poorly nourished, but there was neither clinical nor roentgen evidence of pulmonary tuberculosis. The blood Wassermann and Kahn tests were negative. Rather severe essential hypertension was present, the blood pressure ranging from 205 to 225 systolic and from 105 to 125 diastolic. Several gastric analyses gave the results summarized in table 1.

The patient obtained complete symptomatic relief with the usual treatment for ulcer. The crater decreased in size, as seen in roentgenograms, but did not disappear. Three months later, at operation the hourglass contracture was found, together with a hard ulcer about 0.7 cm. in diameter. The ulcer was excised, examined microscopically and found to be benign. There has been no recurrence of the epigastric distress in the eight years since the operation. The patient has remained well except for the essential hypertension and its complications.

TABLE 1.—*Course of Events in Case 1*

Date	Test Meal	Maximum Free Acidity
Dec. 6, 1930	Motor meal (2 hours)	18
Dec. 12	Ewald (45 minutes)	0
Dec. 15	Alcohol (fractional)	0
Dec. 17	Histamine (fractional)	0
Dec. 22	Normal meal (3 hours)	10
Dec. 31	Histamine (fractional)	12
March 25, 1931	Histamine (fractional)	18

It is of interest to note that one Ewald test meal, one fractional analysis after alcohol and one histamine test each failed to disclose free acidity, although a small amount of free acid had been found previously with a so-called motor meal and was shown to be present by a subsequent histamine test. The level of gastric secretion was obviously low—the lowest in the group studied. It is entirely possible that the gastric secretory response may have been greater at times than the test meals disclosed. The evidence suggests, however, that, while this was not an instance of chronic ulcer with complete achlorhydria, it was a case of chronic ulcer with very low acidity, similar to the case described by Wilson and Earl. The rather indolent, chronic nature of the lesion, with the definite hourglass formation, suggests a process of only moderate activity.

CASE 2.—The course of events in this case is somewhat similar, and in some respects more striking.

A man was first admitted to the clinic in October 1932, at the age of 51. He gave a history of periodic epigastric distress of ten years' duration. The free acidity following an Ewald test meal was 50 degrees. The roentgenograms disclosed a large penetrating ulcer of the lesser curvature of the stomach, with a deep incisura on the greater curvature which almost amounted to an hourglass contracture. Complete symptomatic relief was obtained with medical treatment. The patient soon discontinued the use of alkali, however, and took it only occasionally

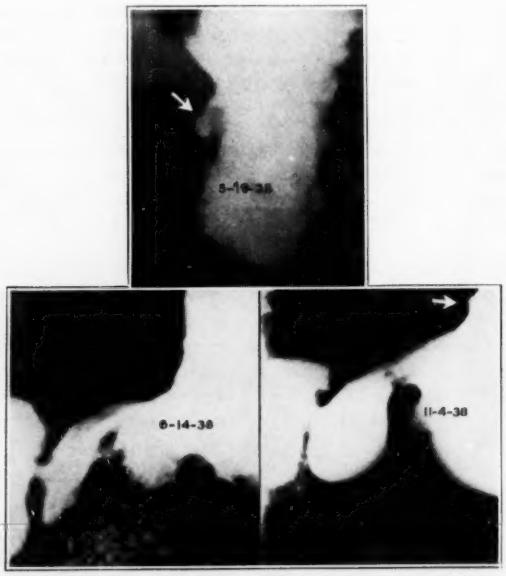


Fig. 3 (case 2).—Chronic gastric ulcer, with hourglass deformity, associated with variable gastric secretory response (transitory achlorhydria demonstrated by histamine tests).

TABLE 2.—*Course of Events in Case 2*

Date	Maximum Degrees of Free Acidity	Gastroscopic Observations	Roentgenographic Observations
1932			
Oct. 5	Ewald..... 50	.....	Large ulcer with hourglass contracture
1933			
May 19	....	.....	Large ulcer
May 25	....	Ulcer with tremendous inflammatory infiltration	.....
May 28	Histamine 0.6 mg. 62	.....	.....
June 1	Histamine 0.6 mg. 33	.....	.....
June 4	Histamine 0.6 mg. 28	.....	.....
June 8	Histamine 1.0 mg. 5	.....	.....
June 15	Histamine 1.0 mg. 0	Two small superficial ulcers with slight inflammation	Very small ulcer with hourglass deformity
June 16	Histamine 1.0 mg. 10	.....	.....
June 27	Histamine 0.6 mg. 45	.....	.....
July 27	....	Ulcer freshly epithelized	.....
Aug. 15	Histamine 0.6 mg. 44	.....	.....
Oct. 8	Histamine 0.6 mg. 64	.....	.....
Oct. 15	Histamine 0.6 mg. 0	.....	.....
Oct. 19	....	Small ulcer with marked gastritis	.....
Oct. 29	Histamine 0.6 mg. 76	.....	.....
Nov. 4	....	.....	Small ulcer with deformity
Nov. 9	Histamine 0.6 mg. 79	.....	.....
Nov. 12	Histamine 0.6 mg. 79	Ulcer ?	Small ulcer with deformity
Nov. 18	....	.....	.....
Nov. 19	Histamine 0.6 mg. 0	.....	.....

whenever slight distress recurred. In 1938, six years later, he returned with another rather severe attack of pain. Roentgenograms again revealed a penetrating gastric ulcer of the lesser curvature, with deformity of the greater curvature also. The Wassermann and Kahn tests of the blood were negative. The patient was thin and poorly nourished, but there was no evidence of extragastric disease. In the course of a few weeks of treatment, the ulcer crater, as seen in the roentgenograms, disappeared (fig. 3). Gastroscopically the ulcer was seen to heal, and the rather intense gastritis improved markedly. Later the ulcer recurred. The course of events is summarized in table 2. As the ulcer healed, the gastric secretory response to histamine decreased from 62 on May 28 to zero on June 15 and then gradually rose to a peak of 79 on November 9. The achlorhydria of October 15 and that of November 19 are difficult to explain. Perhaps they were due to errors in technic. In any event it is apparent that in this case of gastric ulcer there occurred a phase in which gastric secretion was diminished to the point of achlorhydria. During this phase, with continuance of the antacid therapy, the healing of the ulcer progressed and the inflammatory process in the gastric mucosa markedly improved. The hourglass deformity of the stomach in this instance suggests, as in the previous case, a rather indolent or only moderately active process.

The variation in the secretory response to histamine is indeed amazing. Schiff [12] observed the same phenomenon in an apparently normal stomach in which frequent histamine tests were carried out over a prolonged period. The cause was not apparent. The gastric mucosa, as seen through the gastroscope, was not significantly altered during the phase of achlorhydria. Seymour, Spies and Payne [13] also noted that in certain cases the initial histamine test disclosed anacidity but subsequent tests disclosed the presence of free acid.

Case 3.—A woman aged 62 was admitted to the hospital Dec. 7, 1936, complaining that she had experienced continued epigastric pain and vomiting for sixteen days. Periodic gnawing epigastric distress had been present for ten months prior to admission. The fractional gastric analysis after histamine stimulation disclosed a maximum of free acidity of 75 degrees. An enormous penetrating ulcer of the lesser curvature of the stomach was found, and its course to complete healing in April 1937 was followed by means of roentgenograms (fig. 4) and the gastroscope. The course of events is outlined in table 3.

No recurrence of a lesion was found until Oct. 22, 1938, when Dr. Rudolf Schindler observed through the gastroscope a "very definite crater-like, though not very deep, ulcer on the lesser curvature. Its floor was yellowish, its edges were sharp, and it was surrounded by a red halo." It was not seen in the roentgenograms taken on November 1, but on November 16 Dr. Schindler again saw the ulcer, which looked just as it had at the examination one month previously. On December 9 he found that it had healed completely. The patient did not complain of distress during the time the ulcer was present but, on questioning, admitted that she had at times noticed "a little gnawing feeling," relieved by an alkaline powder or by milk.

The lesion recurred in March 1939. The patient did not experience so-called "ulcer pain," although she admitted that on March 4 there was generalized

12. Schiff, L.: Gastric Secretion in Man: Observations on the Effects of Repeated Injections of Histamine and on Transient Achlorhydria, Arch. Int. Med. **61**:774 (May) 1938.

13. Seymour, W. B.; Spies, T. D., and Payne, W.: The Gastric Secretion in Chronic Alcoholic Addiction, J. Clin. Investigation **13**:15, 1939.

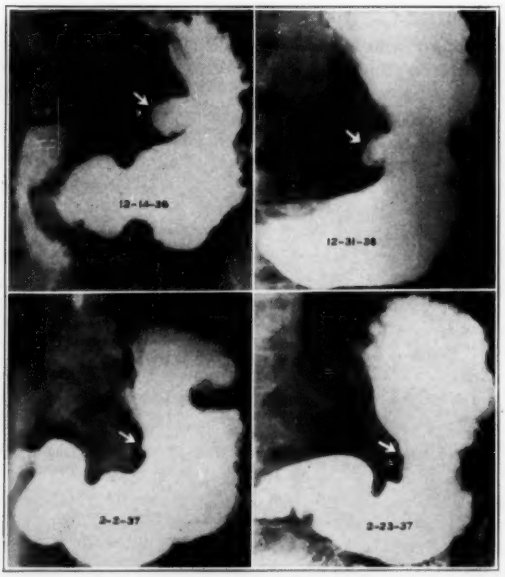


Fig. 4 (case 3).—Chronic gastric ulcer with rapid healing (free acidity at histamine test, 75 degrees).

TABLE 3.—*Course of Events in Case 3*

Date	Maximum Degrees of Free Acidity After 0.5 Mg. Histamine	Gastroscopic Observations	Roentgenographic Observations
December 1936	75	Large ulcer	Enormous ulcer
April 1937 to September 1938 (repeated examinations)	10 to 28	Always healed	Always healed
Oct. 18, 1938	20	.....	.....
Oct. 22	..	Shallow ulcer	.....
Oct. 28	10	.....	.....
Nov. 1	..	.....	Healed
Nov. 11	22	.....	.....
Nov. 16	..	Healing	.....
Dec. 9	..	Healed	.....
Jan. 9, 1939	17	Healed	.....
Feb. 28	4	.....	.....
March 3	..	Shallow ulcer	.....
March 4	0	.....	.....
March 6	..	.....	Very small ulcer (2 mm. in diameter)
March 8	..	Shallow ulcer	.....
March 10	0	.....	.....
March 13	..	.....	Healed
March 15	..	Almost healed	.....
March 20	20	.....	.....
March 27	..	Healed	.....
April 5	0	Healed	.....
April 19	18	Very shallow ulcer	.....
April 21	32*	.....	Very small ulcer (2 mm. in diameter)
April 24	..	Healed	Healed

* Alcohol test meal.

abdominal soreness or discomfort, which was not severe and was somewhat intensified by eating. On the other hand, on March 10 and again on March 15 she stated that there had been no pain—"Nothing bothers me"—and on March 27, when the ulcers were found gastroscopically to be healed, she again admitted the presence of mild epigastric "soreness—just soreness." It was felt that no reliance could be placed on the statements of the patient. She made no complaints at the time of the shallow ulceration found in April 1939. The conclusion was reached that if symptoms were present they were indeed mild.

The free acidity, 75 degrees, present in 1936 at the time the large ulcer was observed is certainly acceptable as acidity. The drop in the gastric secretion and the weak response to histamine after April 1937 are difficult to understand. Per-

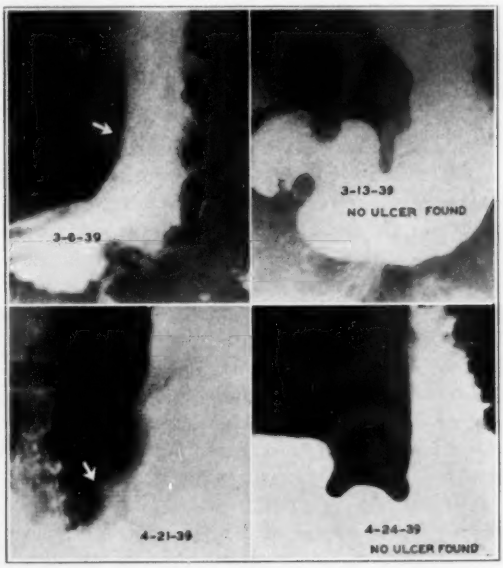


Fig. 5 (case 3).—Acute transitory gastric ulcers, hardly discernible roentgenologically, associated with low gastric acidity and transient achlorhydria.

haps they might be attributed to the atrophic gastritis which Dr. Schindler observed in variable degrees from time to time. The small, shallow ulcer observed gastroscopically on Oct. 22, 1938, during the period of low secretory response, was not found in the roentgenographic examination on November 1. On November 11 gastroscopic examination showed the lesion to be healing, and on December 9 it was healed. Apparently it was a superficial acute or subacute ulcer. A small shallow ulcer was found again by gastroscopic examination on March 3, 1939, and by roentgenologic examination on March 6. It was still seen through the gastroscope on March 8, but the roentgenograms failed to disclose it on March 13. On March 20 it was almost healed, and on April 5 it was healed. A shallow lesion was again visible through the gastroscope on April 19 and could be detected on the roentgenogram two days later. On April 21, however, it could not be

demonstrated by either gastroscopic or roentgenologic examination. No free acid was found after the injection of histamine on March 4, March 10 or April 5, and a maximum of 20 units was found on March 20. This is the most persistently low secretion of acid that we have observed in a patient with ulcer. The lesion demonstrated during the period of achlorhydria and the two occurring in the presence of very low acidity were small, superficial and barely detectable in the roentgenograms (fig. 5), and they healed promptly; hence they seemed obviously to have been acute or subacute rather than chronic ulcers.

COMMENT

Rodgers and Jones [14] recently described a type of acute or subacute small gastric ulcer, 2 to 5 mm. in diameter, which is not found roentgenologically but is found gastroscopically only in the presence of a "thin atrophic mucosa and associated with absence or diminution in the secretion of acid." In 7 of their 17 cases achlorhydria was shown after the injection of histamine (presumably a single test). One of the patients had pernicious anemia and a strongly positive Wassermann reaction. In 3 patients given gastroscopic examination after intervals of two to four weeks, the ulcers were found to have disappeared. The authors stated that they had never seen "large chronic gastric ulcers . . . in patients with a uniformly thin gastric mucosa and either a low acid curve or achlorhydria."

The statement just cited and, indeed, the other observations of Rodgers and Jones are quite in accord with our own experience. Apparently acute and subacute ulcers may develop in the stomach in the presence of achlorhydria, but such lesions do not become chronic nor are they of large size. Acid gastric juice is essential for the development of large chronic ulcers, the typical ulcers of Cruveilhier. Important confirmation of this view is given by the failure of Kahn [15] to find a single chronic, or indeed, acute, peptic ulcer at autopsy in 840 cases of pernicious anemia, and by the apparent failure of Washburn and Rozendaal [16] to find such an ulcer in 906 consecutive cases of pernicious anemia. Murphy and Howard [17] referred to 4 instances of duodenal ulcer encountered in 440 cases of pernicious anemia, but no evidence, clinical or roentgenologic, was presented to show that the alleged ulcer was active.

---

14. Rodgers, H. W., and Jones, F. A.: Subacute Ulceration of the Stomach Associated with Atrophy of the Gastric Mucosa and with Absence or Diminution in the Secretion of Hydrochloric Acid, St. Barth. Hosp. Rep. **71**:140, 1938.

15. Kahn, J. R.: Absence of Peptic Ulcer in Pernicious Anemia, Am. J. M. Sc. **194**:463, 1937.

16. Washburn, R. N., and Rozendaal, H. M.: Gastric Lesions Associated with Pernicious Anemia, Ann. Int. Med. **11**:2172, 1937.

17. Murphy, W. P., and Howard, I.: An Analysis of the Complications Occurring in a Series of Patients with Pernicious Anemia, Rev. Gastroenterol. **3**:98, 1936.

CONCLUSIONS

1. Small acute and subacute gastric ulcers may occur in the presence of achlorhydria proved by the histamine test.

2. Large chronic gastric ulcers occur only in the presence of acid gastric juice.

3. Acid gastric juice plays an essential role in the genesis and course of chronic gastric ulcer.

ADDENDUM

Since the completion of the work just described, a paper by Ruffin and Dick [18] has appeared in which an incidence of achlorhydria in cases of active duodenal ulcer of 5.4 per cent (24 of 419 cases) was reported, as well as a similar incidence in cases of gastric ulcer, 6.7 per cent (3 of 42 cases). Apparently the diagnosis of achlorhydria was based on a single determination (histamine). The fallacy inherent in such an analysis has already been pointed out, but it may be illustrated further by the following brief report:

A man 48 years of age entered the hospital June 7, 1939, with a history of epigastric distress of ten years' duration. The stools had been tarry one month prior to admission. Gastric ulcer was found gastroscopically and roentgenologically. The following gastric analyses were carried out:

Date	Stimulus	Free Acidity (Maximum)
June 15	Histamine, 0.5 mg.	0
18	Histamine, 0.5 mg.	0
24	Histamine, 0.5 mg.	0 (Tip of the tube shown fluoroscopically to be in stomach)
25	Histamine, 0.5 mg.	0 (p_H 3.49)
30	Histamine, 0.5 mg.	52 (p_H 1.50)
30	Histamine, 1 mg.	76 (p_H 1.50)
30	Histamine, 1 mg. and 100 cc. of 7% alcohol	68 (p_H 1.61)

Subtotal gastrectomy was performed by Dr. Phemister July 5. Two small healing gastric ulcers were found in the resected specimen.

In the University Clinics gastric analysis has been carried out for patients with digestive complaints routinely and on the whole with few exceptions during the past twelve years. In a series of over 2,200 cases of proved (roentgenologically, gastroscopically or by operation) active gastric or duodenal ulcer, no instance of complete and persistent achlorhydria has been encountered.

18. Ruffin, J. M., and Dick, M.: The Significance of Gastric Acidity After Histamine Stimulation: A Statistical Study of 2877 Gastric Analyses, Ann. Int. Med. **12**:1940, 1939.

HYDATID CYSTS OF THE LUNG

CAMERON HAIGHT, M.D.
AND
JOHN ALEXANDER, M.D.
ANN ARBOR, MICH.

The infrequent occurrence of hydatids of the lung in North America prompts the recording of 2 cases and a review of the recent literature. Although echinococcus disease is prevalent in Australia, Iceland, South America and some of the Mediterranean countries, only 44 cases of pulmonary and pleural echinococcus cysts are to be found in the literature of the United States and Canada. Thirty-four of these cases were collected in 1930 by Phillips,[1] who added 2 cases of his own. The 8 cases subsequently reported or referred to and the 2 cases reported in this article make a total of 46 known cases.

The nativity of a few of the patients whose cases have been reported is not known; yet it is of interest that hydatid disease of the lung has occurred in only 5 patients known to have been born in North America (Garrett,[2] Magath,[3] Phillips' case,[1] Johns[4] and Leslie[5]). Both the patients who are the subject of this report had emigrated from countries in which the disease is prevalent, and the probability is great that the infestation occurred prior to their entrance into this country. Since the disease may occasionally be encountered in this country, it should be considered in the differential diagnosis of pulmonary lesions resembling hydatid disease. The difficulties in diagnosis are well illustrated in case 2, in which the correct diagnosis was not made until three years after the patient reported for treatment. A discussion of the symptoms, diagnosis and treatment of pulmonary hydatids will be omitted in this article, as these aspects have been fully presented in the

From the Department of Surgery, University of Michigan.

1. Phillips, E. W.: Hydatid Cysts of the Lung: Review of the Recorded North American Cases, Arch. Surg. **21**:1324-1377 (Dec.) 1930.

2. Garrett, R. E.: Hydatid Cysts, with a Report of a Case, Maryland M. J. **49**:373-378, 1906.

3. Magath, T. B.: Echinococcus Disease: Etiology and Laboratory Aids to Diagnosis, M. Clin. North America **5**:549-571 (Sept.) 1921.

4. Johns, F. S., in discussion on Phillips.[1]

5. Leslie, C. J.: Pulmonary Echinococcosis, Am. J. Dis. Child. **55**:1267-1272 (June) 1938.

excellent and comprehensive writings of Phillips,[1] Dew,[6] Dévé,[7] Carayannopoulos [8] and Godfrey.[9]

REPORT OF CASES

CASE 1.—*Hydatids of pleura drained by thoracotomy in another hospital in 1923; reappearance in lung in 1931; operative removal, with apparent cure.*

History.—P. P., a man aged 30, was admitted to the University Hospital on Sept. 16, 1931, complaining of cough, sputum and sweating. The patient was born in Greece, and during his childhood he often played with dogs when visiting his father's sheep ranch. At the age of 14 he emigrated to this country. He was in good health until a year or two later, when he suffered from a cough which was diagnosed as whooping cough. A month after the onset of the cough a sharp pleuritic pain developed in the lower right portion of the chest anterolaterally. He returned to Greece for seven months, and on his arrival there the cough disappeared. Because of continuation of the pain, he was examined by several physicians, whose findings were negative. Roentgenograms of the chest were not taken. On his return to this country, the pain disappeared and he felt well until 1923, when there developed a "cold" and a severe pain of sudden onset in the right side. A diagnosis of pleural effusion was made, and a thoracotomy was performed on the right side. The nature of the observations at operation is not known, as no report could be obtained from the surgeon or hospital. During the daily dressings the patient noticed that numerous whitish gray cysts, 1.5 to 2 cm. in diameter, were expelled from the wound. They were examined, and the patient was told they were echinococcus cysts. The thoracotomy wound became too small for adequate drainage, and a second operation was performed. After this the wound healed, and a roentgenologic examination revealed no further disease. The patient then felt well and had no symptoms except when he had a "cold," at which time there would be a small amount of blood-streaked sputum and occasional mild pain in the region of the thoracotomy scar.

In September 1931, the pain recurred in the right lower portion of the thorax anterolaterally and was accompanied by perspiration, cough and expectoration of dark gray, foul sputum, which had a "burning taste." Eight days later the patient expectorated a "broken cyst," similar in appearance to the cysts which had been discharged through the thoracotomy opening eight years previously. During the next eight days prior to his admission, he expectorated some blood, several cysts and about a cupful of sputum daily.

Physical Examination.—There were marked pallor, profuse diaphoresis, moderate cough and expectoration and less than 1 degree (F.) of fever. Excursion of the right part of the thorax was decreased, and a depressed scar, 5 cm. in length, was visible on this side in the region of the sixth and seventh ribs between the anterior and the posterior axillary line. Extending upward and

6. Dew, H. R.: Hydatid Disease: Its Pathology, Diagnosis and Treatment, Sydney, Australasian Medical Publishing Company, Ltd., 1928; Some Aspects of Echinococcus Disease, Surgery **2**:363-380 (Sept.) 1937.

7. Dévé, F.: Trente-deux années d'étude de l'echinococcose, Prensa méd. argent. **19**:523-534 (Aug.) 1932.

8. Carayannopoulos, G.: Contribution to the Diagnosis and Treatment of Hydatid Cysts of the Lung, Ann. Surg. **100**:125-147 (July) 1934.

9. Godfrey, M. F.: Hydatid Disease: Clinical, Laboratory and Roentgenographic Observations, Arch. Int. Med. **60**:783-804 (Nov.) 1937.

backward from the scar was an area, measuring about 10 by 8 cm., over which there were dulness, absence of breath sounds and decrease in tactile fremitus. The other findings in the physical examination were not significant.

The hemoglobin content was 73 per cent, the white blood cells numbered 11,900 and the blood smear showed eosinophilia (8 per cent). Roentgenograms (fig. 1) disclosed a large, relatively smooth-walled, rounded mass occupying the lower outer quadrant of the right part of the thorax. In the lateral view the mass was seen to be slightly posterior. The right portion of the diaphragm appeared to be drawn upward toward the mass, suggesting the possibility of a communicating track between the liver and the pulmonary mass. On roentgenoscopic examination there appeared to be a definite connection between the mass and the diaphragm (Dr. F. J. Hodges). Examination of the cysts which had been expectorated revealed a laminated wall and many hooklets typical of Taenia echinococcus.

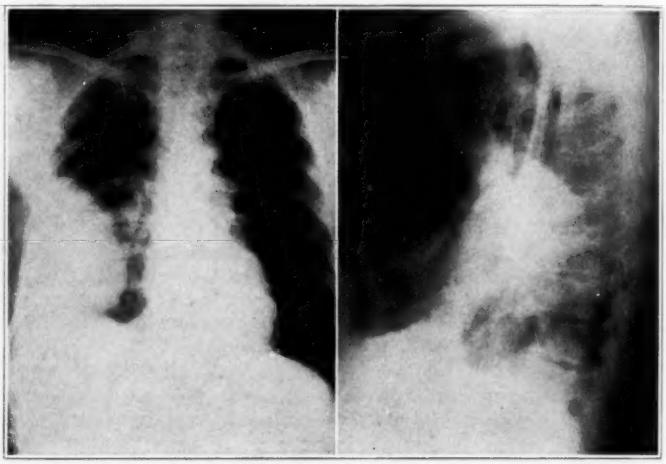


Fig. 1 (case 1).—Frontal and lateral roentgenograms (Sept. 16, 1931) showing area of density in the lower right portion of the chest. Communication with the liver is suggested by the roentgenograms, but was not demonstrated at operation.

Operation.—First Stage of Removal of Pulmonary Echinococcus Cyst (Sept. 17, 1931): An incision was made in the sixth intercostal space and through the parietal pleura anteriorly. The lung was adherent to the thoracic wall only around the site of the previous incision for drainage and slightly superior and posterior to it. In order to cause pleural adhesions to form before the cyst was removed, portions of the fifth and sixth ribs and the intervening intercostal muscle were resected. The exposed parietal pleura was covered with gauze, and the wound was closed without drainage. Pleural effusion developed, and thoracenteses were performed on the fourth, sixth, eighth and fourteenth postoperative days, with the removal of a total amount of 500 cc. of serosanguineous fluid. The second stage of the drainage operation was delayed because of the development of thrombophlebitis of the left leg.

Second Stage; Evacuation of Mother and Daughter Cysts from Base of Right Lung (October 14): The incision was reopened and the gauze pack removed. For complete exposure of the cyst a long segment of the seventh rib was resected. The moment the periosteum was stripped from the posterior surface of this rib, the white wall of the cyst presented and ruptured. The opening into the cyst was enlarged, and approximately fifteen cysts, some filled with fluid and some collapsed, were evacuated. The smallest was approximately 1 cm. in diameter, and the largest, 9 cm. in diameter, was believed to be the mother cyst (fig. 2). The cavity from which these cysts were evacuated contained at least one open bronchus and many small chambers which presumably housed cysts. One of these

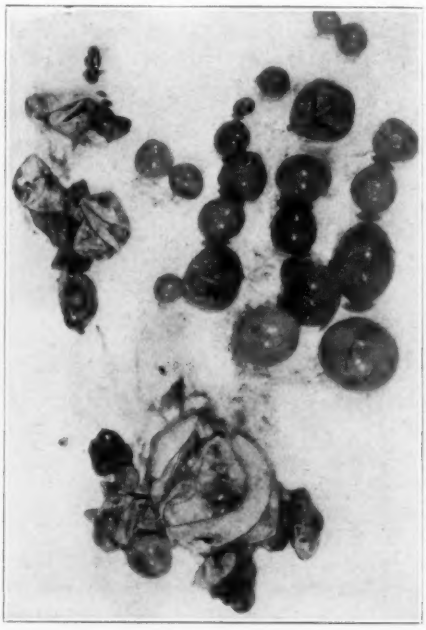


Fig. 2 (case 1).—Mother and daughter cysts removed from pulmonary parenchyma.

chambers communicated with the main chamber only by a narrow track, and on dilatation of its mouth a cyst was evacuated. Inspection of the diaphragmatic aspect of the large defect within the lower lobe of the right lung showed no evidence of communication with the subphrenic space or the liver. In order to obtain complete exposure of the space within the lung, the hitherto unopened portions of the cortex of the lung, which covered the space peripherally, were incised radially between mattress sutures. The space within the lung was wiped with dilute solution of formaldehyde U. S. P. (1:50), as was the extrapleural wound which had been contaminated by the cyst wall. Gauze packs, which had

been treated with petrolatum, were placed in the pulmonary defect, which after the evacuation of the cysts measured approximately 10 cm. in diameter. The anterior and posterior angles of the incision were loosely closed. At the conclusion of the operation it was believed that there was no portion of any cyst wall remaining.

Pathologic examination of the mother cyst showed the wall of an echinococcus cyst with purulent infiltration. The numerous daughter cysts were in various stages of formation. A biopsy specimen of the incised pulmonary tissue lateral to the cyst revealed chronic purulent inflammation and fibroid pneumonia. A biopsy specimen from the thoracic wall did not show animal membrane.

Course.—The postoperative convalescence was uneventful. In order to facilitate the closure of the large pulmonary defect, a temporary interruption of the right phrenic nerve was effected on October 23. The wound closed rapidly, and on

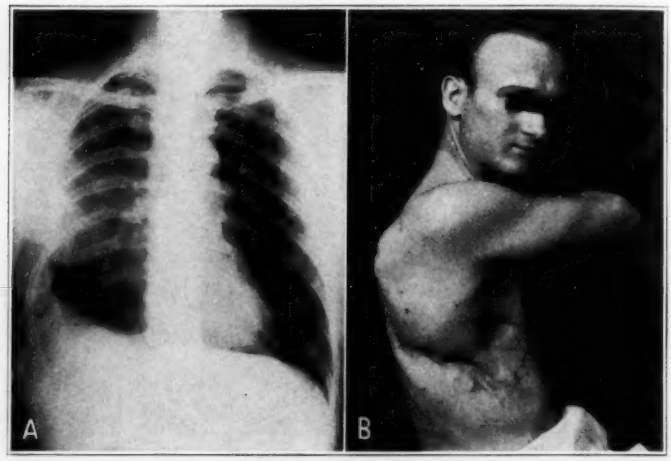


Fig. 3 (case 1).—*A*, roentgenogram taken seven years after operation, showing no evidence of recurrence of cysts. Residual pleural and parenchymal fibrosis is evident. *B*, photograph of patient, showing healed incision.

October 28 the patient was discharged from the hospital, at which time a bronchial fistula was still present. The fistula closed spontaneously after six weeks, and the wound was completely healed one month later. During this period the patient had a small amount (4 cc.) of sputum, which had a "peculiar taste." This symptom disappeared five months after operation. The patient has been examined at intervals during the seven years that have elapsed since operation and has remained without symptoms. The wound is solidly healed. Roentgenoscopic examination shows limitation of function of the lateral portion of the right side of the diaphragm, presumably from adhesions, and roentgenograms show no evidence of recurrence. The patient was last seen on Oct. 24, 1938, at which time a roentgenogram (fig. 3) showed no change when compared with films made in 1934 and 1936.

CASE 2.—*Hydatid cyst of upper lobe of the left lung; spontaneous rupture into bronchus, with secondary infection of cyst; surgical exploration in 1928, with negative results; removal of cyst in 1931; apparent cure.*

History.—C. F., a man aged 25, a Dane, was admitted to the University Hospital in September 1928. In 1921, at the age of 18, he had gone to Argentina, where he remained for twenty months. During this time he worked on a large ranch where there were numerous sheep and dogs. He then came to the United States and had resided here since, being employed as a machinist and chauffeur.

The present illness began in October 1927 with a sharp pleuritic pain in the left side of the chest, located anteriorly near the nipple and posteriorly at the same level. The pain was worse on deep breathing, and there was a severe cough with the expectoration of a small amount of grayish, thick sputum. The symptoms continued until April 1928, when he had a severe coughing spell, during which "it felt like there was something in the chest that wanted to come up." He continued to cough, and suddenly there was a sensation of something being torn loose in the left side of the chest beneath the nipple, followed by a gush of a large amount of "pus," which came from the mouth and nose "as if out of a faucet." The sputum was foul, yellowish, thin and watery. The patient was admitted to a hospital, where, he said, his temperature was 105 F. for several days. His condition gradually improved during a month's hospitalization, but the pain, cough and expectoration of foul sputum continued. In July 1928 hemoptyses began, and pneumothorax therapy was instituted. The pneumothorax aggravated the hemoptyses and was promptly discontinued. Operation was advised.

Physical Examination.—The patient was well nourished. There were flatness on deep percussion, diminution of the voice and breath sounds and decreased excursion of the upper left portion of the chest in an area between the third and the sixth rib anteriorly. No rales were present; the heart was not displaced. The temperature was 99 to 100 F., the pulse rate 90 to 100, the respiratory rate 20 and the white cell count 13,200. Roentgenologic examination revealed what appeared to be a large collection of fluid in the upper left part of the chest. A preoperative diagnosis of interlobar empyema with bronchial fistula was made.

First Operation (Sept. 20, 1928).—With the use of local anesthesia, exploratory thoracotomy was performed through an anterior axillary approach, with the removal of 10 cm. of the fifth rib. Air from the recent pneumothorax was present in the pleural cavity. The upper lobe was adherent to the anterior thoracic wall. The lower lobe was adherent inferiorly and posteriorly, where it seemed infiltrated on palpation, and over this area of apparent infiltration aspiration was performed through the intact skin. No pus was found. The interlobar fissure was opened to the hilus of the lung without the finding of any fluid or abscess. Although no induration of the upper lobe was palpable through the thoracotomy incision, aspiration was likewise carried out through the intact skin in the region of the upper lobe where it was adherent to the thoracic wall, and no pus was found. It was then concluded that a pulmonary abscess rather than interlobar empyema was present and that the abscess was so small that it could not be palpated. The wound was closed, and the air from the pneumothorax was evacuated.

Course.—The postoperative course was uneventful, and roentgenologic examination showed that the rounded mass seen previously had lost its definite contour. The patient was discharged on October 2. He had gained in weight and felt considerably improved.

In the interval between 1928 and his readmission in 1931, the patient worked regularly, and during most of the time he felt fairly well. He continued how-

ever, to expectorate a small amount of sputum, about 4 Gm. daily, which had an offensive taste and was occasionally blood streaked. In February 1929, a diagnostic bronchoscopic examination showed inflammation of the left bronchial tree. During the several months preceding his readmission to the hospital on Oct. 13, 1931, there had been an increase in the amount of sputum, which was foul and occasionally bloody, a loss of 10 pounds (4.5 Kg.) in weight, fever (101.5 F.), general malaise and weakness. Two weeks before his readmission he mentioned that he had expectorated a "piece of skin" which was "smooth on one side and pussy on the other," and hydatid disease was then suspected for the first time. Further questioning revealed that in January 1929 he had first coughed up "a piece of skin which was very thin, like the inside of an egg shell, and twice the size of one's thumbnail." At intervals of from one to three months he had coughed up these pieces of "skin," which gradually became larger and thicker. They were raised unexpectedly and were not preceded by a paroxysm of coughing.

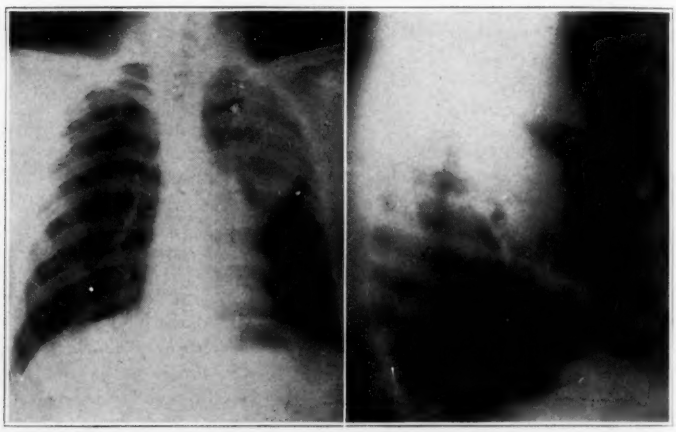


Fig. 4 (case 2).—Frontal and lateral roentgenograms (Oct. 16, 1931) showing area of density in the upper lobe of the left lung and in the region of the superior portion of the interlobar fissure.

Examination.—The results of physical examination were essentially negative except for an area of dulness between the third and the sixth rib in the left anterior axillary line. On roentgenologic examination (fig. 4) a diffuse, somewhat homogeneous area of increased density, which was slightly nodular at its upper margin, was seen anteriorly, extending from the first rib to the third intercostal space. The sputum did not contain tubercle bacilli or hooklets. The complement fixation test for Echinococcus gave negative results.

Second Operation.—Removal of Echinococcus Cyst in Upper Lobe of Left Lung (Oct. 19, 1931): The axillary portion of the third rib was removed. The pleurae were adherent, and exploratory puncture produced heavy, whitish yellow material at a depth of 1 cm. in the lung. The thickened pleura and lung were widely opened with the actual cautery, and immediately cyst membranes began to bulge. The cyst wall was very friable, and all the small and large pieces were completely

shelled out. There was no evidence of daughter cysts. The wall of the remaining cavity, being formed by the pulmonary tissue, bled moderately, and in various portions of the medial portion of the wall there were bronchial openings of medium size. The pulmonary cavity was wiped with dilute solution of formaldehyde U. S. P. (1:50) and packed with gauze that had been treated with petrolatum. The wound in the thoracic wall was irrigated with the solution of formaldehyde and packed wide open.

Pathologic examination of the cyst wall showed fine laminations, characteristic of echinococcus cysts (fig. 5). The cyst wall was largely necrotic and in part showed leukocytic infiltration. No heads or hooklets were seen.

Course.—The postoperative convalescence was uneventful. On October 28, a temporary interruption of the left phrenic nerve was made to aid in closure of the

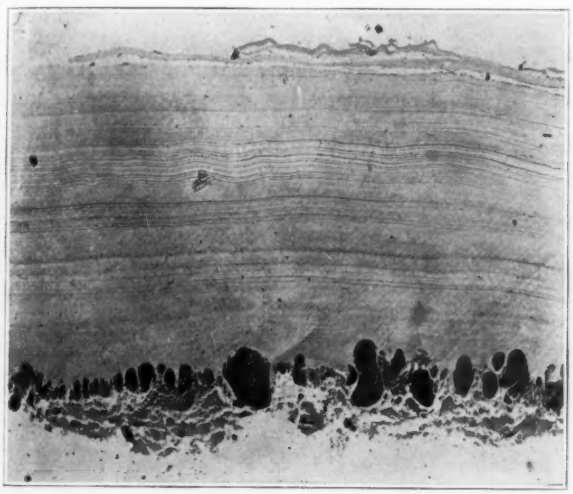


Fig. 5 (case 2).—Photomicrograph showing typical laminated wall of an echinococcus cyst (× 33).

pulmonary defect. The patient was discharged from the hospital November 28, at which time there remained a bronchial fistula, which closed spontaneously two weeks later. Since closure of the fistula there has been no cough or sputum. The patient returned to work on Jan. 10, 1932. Periodic examination since operation has not revealed any evidence of recurrence. He continues to feel well, and there is no cough or expectoration. Roentgenologic examination on Nov. 26, 1937 (fig. 6) showed scattered areas of pleural and pulmonary fibrosis, which were identical with similar areas seen in roentgenograms made in 1932 and 1933.

CASES REPORTED IN THE RECENT LITERATURE

The following cases of hydatid cysts of the lung have been reported since the publication, in 1930, of Phillips' collected series. The dates in parentheses are those on which the report was made.

JOHNS'S CASE[4] (1930).—A Virginian who had been in the World War for two years returned with the complaint of considerable loss of weight. A "tumor" of the right lung was seen in roentgenograms, and at operation a calcified cyst, about the size of an orange, was removed. The diagnosis was uncertain. About one year later an infection developed in the pleura, and the diagnosis was then confirmed by the finding of hooklets. After excision of the involved pleura the patient made a complete recovery.

It appears likely that the disease in Johns's case developed while the patient was residing in this country, and prior to the two years spent in the World War. This deduction is based on several premises. One is the prevalence of echinococcus disease in domestic animals in Virginia. In 1917, Johnston and Willis[10] reported the occurrence of several epidemics among hogs in Virginia from 1913 to 1914, and they mentioned infestation of 25 per cent of 60 hogs shipped from Charlotte County in November 1917. Also, the latent period before

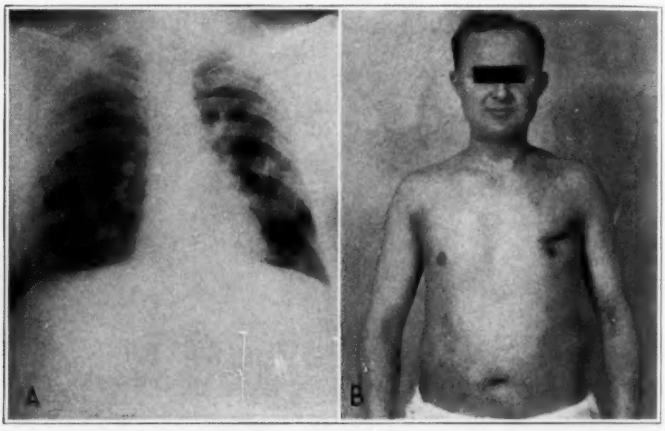


Fig. 6 (case 2).—*A*, roentgenogram taken six years after operation, showing no evidence of recurrence of cysts. *B*, photograph of patient. The cyst was removed through the upper incision (healed). The lower inframammary incision was the site of the "negative" exploration in 1928.

the development of symptoms is notably long in many cases of echinococcus disease, and the finding of a calcified cyst in this case suggests that the latent period was longer than the two years of the patient's service in the World War.

LILIENTHAL'S CASE[11] (1930).—In the discussion of Phillips' paper, Lilienthal merely stated that he had had 1 case of hydatid cysts of the lung, in which the patient was born in Greece and left there when he was very young. Lilienthal mentioned another case, one of a possible retrosternal hydatid cyst, which is not included with the collected cases presented in this article because the diagnosis was uncertain and the location was neither in the lungs nor in the pleura.

---

10. Johnston, G. B., and Willis, M.: Hydatid Cyst of the Liver with Report of Two Cases, Surg., Gynec. & Obst. **25**:101-103 (July) 1917.

11. Lilienthal, H., in discussion on Phillips.[1]

ZOHLEN'S CASE[12] (1930).—The case was one of echinococcus cysts of the abdomen and lung in a 46 year old Greek who had come to this country at the age of 25. At the age of 41 he had had an operation for tumors of the abdomen in which, he stated, "the doctor drew water off the tumors." At operation, Zohlen found three cystic tumors in the abdomen. Numerous daughter cysts were removed from the cysts. Pathologic examination revealed that the wall of the cyst was typically laminated, but no hooklets were seen. No attempt was made to aspirate or to remove the cyst from the right side of the chest, and accordingly the diagnosis of the thoracic lesion was not verified.

Roentgenograms of the chest which are reproduced in Zohlen's article show changes consistent with hydatid disease, and in view of the abdominal cysts, it must be assumed that such a diagnosis is the most likely.

HEUER AND ANDRUS' CASE[13] (1930).—These authors observed 2 instances of hydatid cyst of the liver and "one of pleural or rather parapleural cyst." No details of this case were given.

GRAHAM, SINGER AND BALLON'S CASE[14] (1935).—A man aged 39, who had been a butcher for four years previous to the onset of his illness, and who during the four years immediately preceding this period had been in contact with dead dogs, sheep and other animals in England, complained of cough, dyspnea and expectoration of "pinkish" material of twelve years' duration. A portion of the left ninth rib was resected in 1923, and a typical echinococcus cyst of the pleura, which communicated with similar processes in the lung, was then discovered. There were many daughter cysts and hooklets in the pleura. The patient was treated for an echinococcus cyst of the liver one year later. The authors stated that the lesion in the liver was undoubtedly the primary one. Reexamination in 1927 showed that the patient was in good health. (This case was included in a report by Andrus[15] in 1935.)

NEUHOF'S CASE[16] (1937).—A child aged 13 years had a pulmonary hydatid cyst of six months' duration. At the onset the diagnosis of bronchopneumonia was made, and pus was obtained on two diagnostic aspirations of material from the chest. Fever, cough and expectoration of purulent material continued. The roentgenogram made on admission for treatment showed a homogeneous shadow with a fluid level. At operation, shortly after admission, an elastic mass in the substance of the lower lobe of the right lung was exposed. It was packed off, and at the second stage, one week later, it was entered. There was a fibrous shell of tissue overlying a cyst within the substance of the lung. The cyst contained purulent fluid, which was evacuated. The collapsed cyst wall could then be removed without difficulty. After its removal there were noted a number of large and small bronchial fistulas. The pathologic report on examination of the

12. Zohlen, J. P.: Echinococcus Cysts of Abdomen and Lung: Case Report, Wisconsin M. J. **29**:515-517 (Sept.) 1930.

13. Heuer, G. J., and Andrus, W. DeW., in Lewis, D.: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1930, vol. 5, chap. 5, p. 161.

14. Graham, E. A.; Singer, J. J., and Ballon, H. C.: Surgical Diseases of the Chest, Philadelphia, Lea & Febiger, 1935, pp. 752-753.

15. Andrus, W. DeW.: Report of the Chest Tumor Registry, J. Thoracic Surg. **4**:236-250 (Feb.) 1935.

16. Neuhof, H.: The Free Transplantation of Fat for the Closure of Bronchopulmonary Cavities (Lattice Lung), J. Thoracic Surg. **7**:23-24 (Oct.) 1937.

cyst wall was that of infected echinococcus cyst. The wall of the pulmonary cavity soon became clean and rigid, and the bronchial fistulas persisted. One month after the primary operation, the bronchopulmonary cavity was closed with a free transplant of fat. The patient was reported to be free from symptoms.

LESLIE'S CASE[5] (1938).—A 7 year old boy, American born of Italian descent, had echinococcus cysts in both lungs. Two years previous to the onset of symptoms he had spent some time on a farm in Italy and while there had had a pet dog. The symptoms were recurrent attacks of fever, with a temperature as high as 105 F., for three weeks; slight, nonproductive cough; mild night sweats, and some loss of weight; there was no hemoptysis. At the onset of symptoms he was confined to bed because of weakness, but he had been up and about for one week before his admission to the hospital. Five months before this he had been ill with pneumonia for two months. A roentgenogram showed a large, circumscribed area of density, apparently due to encapsulated fluid, in the lower lobe of the left lung. In the lower lobe of the right lung an area of density about 2.5 cm. in diameter was seen. Thoracentesis was carried out on the left side, because of the impression that the patient had encapsulated empyema. Clear, watery fluid under slight pressure was obtained. It did not contain cells, globulin or hooklets. After the thoracentesis there developed a violent pleural reaction, with toxicity, a temperature of 103 F., pain and friction rub. A roentgenogram at this time showed a large, thick-walled cyst in the left lung, with hydropneumothorax on the left side. The cyst contained only a small amount of fluid. Apparently the contents had escaped into the pleural cavity. The complement fixation test for Echinococcus gave a strongly positive reaction. Thoracotomy, with resection of the eighth rib, was performed. Removal of the cyst and marsupialization of the cavity were found to be impracticable, and simple drainage by tube was established. The tube was removed on the ninth day. The prognosis was considered poor because the cyst had not been removed, because the hydatid fluid (presumably infective) had been disseminated throughout the pleural space and because the lesion in the right lung was presumably another cyst. A roentgenogram made five weeks after operation showed reexpansion of the left lung with definite reduction in the size of the cyst. The cyst in the right lung appeared slightly larger than before. The patient was readmitted to the hospital about two months later because of adbominal pain and vomiting, and operation revealed a perforated gangrenous appendix with generalized peritonitis. The postoperative course was stormy, and the patient died fourteen days after operation. Permission for necropsy was refused. At no time during his illness previous to the appendicitis was there evidence of a lesion in any organ other than the lungs.

CRAVER AND BRINKLEY'S CASE[17] (1939).—In an article on aspiration for the diagnosis of suspected bronchogenic carcinoma, the author stated that the diagnosis of echinococcus cyst was made in 1 case.

COMMENT

The nativity of patients in 9 of the 46 reported cases of echinococcus cysts of the lung and pleura is not known. In 32 of the reported cases the patients had emigrated to North America. In 5 instances the disease occurred in persons born in the United States. The patient in Garrett's

17. Craver, L. F., and Brinkley, J. S.: Aspiration Biopsy of Tumors of the Lung, J. Thoracic Surg. **8**:436-461 (April) 1939.

case,[2] a Negro woman aged 46, a native of Maryland and an inmate of the state asylum for about seventeen years, had apparently never traveled outside this country; the diagnosis was definitely established in this case by the demonstration of hooklets. In Phillips' case 1 the patient had never been outside the state of New York. Although the

Nativity of Patients in Cases of Hydatid Cysts Reported in North America

Author	Date Reported	Nativity of Patient
Gay	1858	Not mentioned
Stille	1858	Not mentioned
Smith, F. G.	1858	Not mentioned
Minot	1859	Not mentioned
Loomis	1879	Ireland
Ainsworth	1880	Poland
Fenger and Hollister	1881	Italy
Smith, D. F.	1882	Not mentioned
Bernay	1882	England
Black	1882	England
Ferguson	1893	Not mentioned
Keyes and Busch	1896	Germany
Beck	1898	Austria
Chown	1901	Iceland
Gay	1901	Italy
Stone	1903	Armenia
Gurlee	1905	Italy
Senn	1905	Greece
Garrett	1906	United States
Smith and Harrington	1907	Russia
MacDonald	1913	New Zealand
Ramey and Emerson	1915	Greece
Davis and Balboni	1917	Italy
Clarkson (case 1)	1917	Macedonia
Clarkson (case 2)	1917	Italy
Crow	1918	Spain
Magath	1921	United States
Balboni (case 1)	1922	Greece
Balboni (case 2)	1922	Greece
Mills	1922	France
Glassman	1922	Siberia
Curran and Locke	1924	Syria
Campbell	1925*	Russia
Ortenberg †	1929	Russia
Phillips (case 1)	1930	United States
Phillips (case 2)	1930	Italy
Johns	1930	United States
Lilienthal	1930	Greece
Zohlen	1930	Greece
Heuer and Andrus	1930	Not mentioned
Graham, Ballon and Singer	1935	England
Neuhof	1937	Not mentioned
Leslie	1938	United States
Craver and Brinkley	1939	Not mentioned
Haight and Alexander	1939	Greece
Haight and Alexander	1939	Denmark

* References to the cases reported up to this date and the nativity of the patients are given in the article by Phillips.[1]

† The reference to Ortenberg's case is given by Phillips.[1] The nativity of the patient in this case is mentioned by Young (Canad. M. A. J. **13**: 48, 1923).

remaining 3 native-born patients had traveled outside the United States, it is probable that 1 of these patients (Johns's case) had contracted the disease in this country. The patient reported on by Magath [3] was born in the United States and had lived in Nebraska, but had traveled in the Philippine Islands in 1908. In this case, as well as in Leslie's case, it cannot be stated whether or not the disease originated while the patient was in this country; it is possible that infestation may have occurred during residence elsewhere.

During the past twelve years, 6 patients with verified echinococcus disease of the abdominal cavity have been treated in the University Hospital. The country of birth of these patients is as follows: Greece, 2; China, Austria, Bulgaria and Russia, 1 each. All of the patients had hepatic cysts. One also had cysts in the gastrocolic omentum and the pelvis, and another, cysts of the abdominal cavity, pelvis and abdominal wall. The involvement of the abdominal wall had undoubtedly resulted from an operation fifteen years previously. Another patient, an Italian, who refused operation and the diagnosis of whose condition was not verified, presented a calcified cyst of the liver; the complement fixation test for echinococcus disease gave a doubtful positive reaction, but the antigen used was at least one year old.

It is of interest that the reports of cases of echinococcus disease in native-born North Americans continue to be rare, especially in view of the presence of hydatid disease in domestic animals. In 1930, Phillips quoted a personal communication from Maurice C. Hall, chief of the Zoological Division, Bureau of Animal Industry, United States Department of Agriculture, Washington, D. C. Hall reported that figures regarding the incidence of hydatid disease in domesticated animals in this country are not available, and added:

> In general, it may be said that hydatids are not generally distributed throughout the United States and that they have a patchy distribution, not well known. They are said to be prevalent in parts of New Mexico, Oklahoma and Arkansas; we can always obtain them on rather short notice from our inspection service at Richmond, Virginia; they are found from time to time at various abattoirs. In 1927, Morris reported that hydatids occurred in 5 per cent of swine at Baton Rogue, and that the former incidence was 20 per cent. Dr. Jalen, our inspector at Cincinnati, Ohio, reported in 1927 that less than 1 per cent of swine at that station were affected.

In more recent personal communications (Aug. 13 and 19, 1936) from Benjamin Schwartz, chief of the Zoological Division, Bureau of Animal Industry, a similar situation was reported. Schwartz stated:

> During the fiscal year ended June 30, 1936, 1,513 cattle livers and 21 calf livers were condemned on account of infestation with Echinococcus. Echinococcus infestation is not rare in swine in certain sections of the United States, particularly in the South. We have no difficulty in securing such material from abattoirs in Richmond, Va. We have been informed recently that Echinococcus in the liver of swine is fairly common in abattoirs in Nashville, Tenn.

A personal communication (Oct. 3, 1933) from C. H. Clark, state veterinarian, Department of Agriculture, Lansing, Mich., stated:

> To my knowledge, no special investigations have been made in this state regarding the incidence of echinococcus disease in sheep, dogs or other domestic animals. I have never had the opportunity of seeing it in Michigan.

SUMMARY

Two cases of echinococcus disease of the lungs are presented, and the nativity of the patients in the 46 cases of hydatid disease of the lungs and pleura reported in the North American literature is reviewed. The disease has occurred in only 5 persons known to have been born in North America. Certain epidemiologic aspects of the prevalence of hydatid disease in domestic animals in this country are mentioned.

THE COLLOIDAL GOLD REACTION OF BLOOD SERUM IN DISEASES OF THE LIVER

SEYMOUR J. GRAY, M.D.
CHICAGO

The purpose of this paper is to report studies of the colloidal gold reaction of blood serum in diseases of the liver. Zsigmondy,[1] in 1901, laid the foundation for the diagnostic use of the colloidal gold reaction by observing that "certain colloids, especially proteins," prevented the precipitation of colloidal gold suspensions by electrolytes, each protein exerting a specific degree of protection against precipitation. On the other hand, Lange,[2] in 1912, found that proteins within certain dilutions did not prevent but actually caused the precipitation.

The mechanism of the colloidal gold reaction has been the subject of much investigation. Numerous workers, including Felton,[3] Weston,[4] Cruickshank [5] and others,[6] have shown that the globulin content is the determining factor in the precipitation of colloidal gold and that albumin protects the colloidal suspension from precipitation. The varying colloidal gold curves obtained with spinal fluids in different pathologic conditions result from variations in the balance between the precipitating activity of the globulin and the protective action of the albumin. There is evidence, moreover, that the individual globulin fractions, particularly

From the Department of Medicine of the School of Medicine of the Division of Biological Sciences, the University of Chicago.

1. Zsigmondy, R.: Die hochrothe Goldlösung als Reagens auf Colloide, Ztschr. f. anal. Chem. **40**:697, 1901.

2. Lange, C.: Die Ausflockung von Goldsol durch Liquor cerebrospinalis, Berl. klin. Wchnschr. **49**:897, 1912; Die Ausflockung kolloidalen Goldes durch Cerebrospinalflüssigkeit bei luetischen Affektionen des Zentralnervensystem, Ztschr. f. Chemotherap. **1**:44, 1912.

3. Felton, L. D.: Cerebrospinal Fluid and the Colloidal Gold Reaction, New York State J. Med. **105**:1170, 1917; A Study of the Specificity of the Colloidal Gold Reaction from the Physicochemical Standpoint, Tr. Sect. Path. & Physiol., A. M. A., 1917, p. 73.

4. Weston, P. G.: The Colloidal Gold Reaction, Am. J. Syph. **3**:266, 1919; The Nature of the Substance Causing the Colloidal Gold Reaction, Am. J. Insan. **76**:393, 1920.

5. Cruickshank, J.: The Value and Mechanism of the Colloidal Gold Test, Brit. J. Exper. Path. **1**:71, 1920.

6. (*a*) Vogel, K. M.: The Nature and Interpretation of the Colloidal Gold Reaction, Arch. Int. Med. **22**:496 (Oct.) 1918. (*b*) Mayr, J. K.: Zur Theorie und Praxis der Kolloidreaktionen mit besondern Berücksichtigung der Goldsolreaktion, Arch. f. Dermat. u. Syph. **144**:200, 1923.

the euglobulins, play an important role in the precipitation of colloidal gold. Kafka and Samson [7] and Haug [8] concluded that the reaction depends primarily not on the quantitative increase in globulin but on the qualitative alteration in the globulin fractions. Reznikoff [9] reproduced different colloidal gold curves by varying the relative concentrations of the euglobulin, pseudoglobulin and albumin. Fischer [10] expressed the belief that the euglobulin and pseudoglobulin fractions have the strongest precipitating action on colloidal gold solutions. Mellanby and Anwyl-Davies,[11] Reznikoff [9] and Spiegel-Adolph [12] observed that the euglobulin fraction exerts a considerable influence on precipitation.

The present studies of the colloidal gold reaction of blood serum in hepatic disease were instigated by observations that alterations in the plasma proteins,[13] particularly in the euglobulin fraction,[14] are frequently

7. Kafka, V., and Samson, K.: Die Eiweissrelation des Liquor cerebrospinalis: Eiweissrelation und Kolloidreaktionen, Ztschr. f. d. ges. Neurol. **117**: 128, 1928.

8. Haug, K.: Untersuchung zur Frage der Beziehungen zwischen Goldsolreaktion, Zellgehalt, und Eiweissrelation nach Kafka im Liquor cerebrospinalis, Ztschr. f. d. ges. Neurol. u. Psychiat. **149**:103, 1933.

9. Reznikoff, P.: The Action of Proteins and Blood Serum on Colloidal Gold Solutions and Its Quantitative Interpretation, J. Lab. & Clin. Med. **8**:92, 1922.

10. Fischer, H.: Ueber den Mechanismus der Goldsolreaktion im Liquor cerebrospinalis, Ztschr. f. d. ges. exper. Med. **14**:60, 1921.

11. Mellanby, J., and Anwyl-Davies, T.: The Precipitation of Colloidal Gold by Cerebrospinal Fluid: The Diagnosis of Neurosyphilis, Brit. J. Exper. Path. **4**:132, 1923.

12. Spiegel-Adolph, M.: Physikalisch-chemische Untersuchungen bestrahlter Proteine: Die Veränderungen des Seralbumins bei Ultraviolettbestrahlung und ihre Beziehungen zur Hitzegerinnung, Biochem. Ztschr. **186**:181, 1927.

13. (*a*) Grenet, H.: Diminution des albumines du sérum sanguin chez les hépatiques, Compt. rend. Soc. de biol. **63**:552, 1907. (*b*) Gilbert, A., and Chiray, M.: Diminution des substances albumineuses du sérum sanguin chez les cirrhotiques ascitiques, ibid. **63**:487, 1907. (*c*) Felinski, W.: L'augmentation de taux de la globuline dans le sérum du sang, Presse méd. **20**:236, 1922. (*d*) Abrami, P., and Wallich, R.: Modifications du sérum sanguin au cours des cirrhoses du foie avec ascites: Inversion du rapport sérums-globulines, Compt. rend. Soc. de biol. **101**:291, 1929. (*e*) Snell, A. M.: Changes in Proteins of Blood in Hepatic Disease, Proc. Staff Meet., Mayo Clin. **10**:489, 1935. (*f*) Myers, W. K., and Keefer, C. S.: Relation of Plasma Proteins to Ascites and Edema in Cirrhosis of the Liver, Arch. Int. Med. **55**:349 (March) 1935. (*g*) Foley, E. F.; Keeton, R. W.; Kendrick, A. B., and Darling, D.: Alterations in Serum Proteins as an Index of Hepatic Failure, ibid. **60**:64 (July) 1937. (*h*) Tumen, H., and Bockus, H. L.: The Clinical Significance of Serum Proteins in Hepatic Disease, Am. J. M. Sc. **193**:788, 1937.

14. (*a*) Gros, W.: Zur Frage gesetzmässiger Veränderungen des Bluteiweissbildes beim multiplen Myelom, Deutsches Arch. f. klin. Med. **177**:461, 1935.

(Footnote continued on next page)

associated with diseases of the liver, and by the fact that the euglobulin fraction has been shown to play an important role in colloidal gold precipitation.[15]

The colloidal gold reaction of the blood serum was studied in 96 cases of diseases of the liver: 46 cases of cirrhosis, 14 of acute parenchymatous disease, 25 of neoplastic involvement and 11 of miscellaneous diseases. The diagnoses were confirmed by autopsy, biopsy or laparotomy in 11 cases in the first group, 2 in the second, 13 in the third and 8 in the fourth. A control series and a series of 20 cases of syphilis without clinical evidence of liver disease were studied also. The control series included 95 patients. Twenty of these were normal adults, and 75 had various extrahepatic diseases. Normal livers were found at autopsy, biopsy or laparotomy in 22 patients.

In addition to the colloidal gold tests, the chemical studies of the blood included determinations of the plasma albumin, globulin, cholesterol, cholesterol esters and fibrinogen. The Takata-Ara, bromsulphalein retention, and galactose tolerance tests and other tests of hepatic function were also carried out in many cases.

METHODS

The colloidal gold solution is prepared and acidified in accordance with Klaas's modification of Patterson's [16] method, as used routinely in the serology laboratroy of the University of Chicago Clinics. The amount of fiftieth-normal hydrochloric acid to be added to the colloidal gold solution is determined with alizarin red as indicator and is checked further by control tests with serums from normal persons and with "known positive" serums from patients known to have hepatic disease. The sensitivity of the reaction may be increased or decreased by increasing or decreasing the acidity of the solution. Standardization need be done only once for each supply of colloidal gold prepared, since several liters may be kept for as long as two months without changing the acid requirement. Immediately before each test is performed acid is added drop by drop, the solution being constantly agitated. Usually from 1.1 to 1.7 cc. of fiftieth-normal hydrochloric acid is needed for every 50 cc. of colloidal gold used. The p_H is usually about 7, varying with the individual colloidal gold preparation.

Immaculately clean pyrex glassware should be used throughout the procedure.

(*b*) Kendall, F. E.: Studies on Serum Proteins: I. Identification of a Single Serum Globulin by Immunological Means; Its Distribution in the Sera of Normal Individuals and of Patients with Cirrhosis of the Liver and with Chronic Glomerulonephritis, J. Clin. Investigation **16**:921, 1937. (*c*) de Vries, A.: On the Connection Between the Takata-Jezler Reaction and Its Variant, the Mancke-Sommer Reaction, and the Globulin Fractions of the Blood, Acta med. Scandinav. **98**:95, 1938.

15. Reznikoff.[9] Fischer.[10] Mellanby and Anwyl-Davies.[11] Spiegel-Adolph.[12]

16. Patterson, J.: Preparation of Colloidal Gold, Brit. J. Exper. Path. **12**: 143, 1931.

Five cubic centimeters of venous blood is obtained from the patient before breakfast and centrifuged; 0.1 cc. of clear serum is removed and diluted 1:350 with physiologic solution of sodium chloride. In the first of a series of ten tubes is placed 1.8 cc. of a 0.3 per cent solution of sodium chloride. In each of the following nine tubes is placed 1 cc. of a 0.3 per cent solution of sodium chloride. Then 0.2 cc. of the diluted serum is added to the first tube of the series. The contents are mixed, and 1 cc. is then transferred to the second tube and mixed. This procedure is followed throughout the series of ten tubes, and 1 cc. of the mixture in the last tube is discarded. Five cubic centimeters of acidified colloidal gold solution is added to each tube, and the readings are made after twelve to twenty-four hours.

In reading the test the same numbers are used as in reading the regular Lange reaction: 0, red; 1, red-blue; 2, orchid; 3 blue; 4, light blue; 5, colorless.

The greater the precipitation of the colloidal gold, the higher the numbers; 5 represents complete precipitation. The normal range in our experiments varied from 0000000000 to 3332210000. The number 3 appears only occasionally on the left side of the curve. The positive reaction is similar to the dementia paralytica type of curve obtained with spinal fluid—for example, 5532100000 or 5432100000.

RESULTS

Cirrhosis of the Liver.—The colloidal gold reaction of the serum was positive in all 46 cases of cirrhosis of the liver. The type and severity of the disease varied. The diagnosis was confirmed by autopsy or biopsy in 11 cases (table 1).

The plasma proteins were studied in 39 of the 46 cases in this group. The globulin was increased to an average of 3.19 Gm. per hundred cubic centimeters (normal range: 1.5 to 2.8 Gm.). Increased values were noted in 23 cases, more frequently in advanced hepatic disease than in early cirrhosis. A decrease in albumin was observed in 26 cases, with an average value of 3.50 Gm. for the group (normal range 4 to 6 Gm.). Low plasma albumin values were associated more closely with the severity and duration of the hepatic disease than with the presence of ascites. Increases in globulin compensated for the decrease in albumin in all but 9 cases, so that the average value of the total plasma proteins was within normal limits (6 to 8 Gm.). Abnormally low or inverted albumin-globulin ratios were found in 28 cases; this fact is in accord with the numerous observations [12] on the frequency of variation of the plasma protein content in hepatic diseases. Although positive colloidal gold reactions were associated in a considerable number of cases with abnormal plasma protein values, they were also obtained for 16 plasmas with normal globulin concentrations, and for 11 with normal albumin-globulin ratios.

The total plasma cholesterol, determined in 39 cases, was normal (140 to 200 mg. per hundred cubic centimeters) in 20, increased in 7 and decreased in 12 cases in which severe hepatic damage was predominant. The plasma cholesterol esters, determined in 36 cases, were

TABLE 1.—*Data on the Blood in Cirrhosis of the Liver*

Case No.	Patient	Serum Colloidal Gold Reaction	Plasma Albumin/ Globulin, Gm. per 100 Cc.	Plasma Fibrinogen, Gm. per 100 Cc.	Plasma Cholesterol/ Cholesterol Esters, Mg. per 100 Cc.	Wassermann Test	Takata-Ara Test	Van den Bergh Reaction and Icteric Index	Galactose Tolerance, Bromsulphalein Retention and Other Tests	Diagnosis
1	W. Z.	5544531000	3.54/4.21	....	168/79	Neg.	.....	Direct—faint delayed Indirect—normal	Gal. tol.—1.3 Gm. Brom.—60 per cent	Portal cirrhosis
2	B. F.	5553310000	.....	....	.....	Neg.	.....	Icteric index 63	.....	Portal cirrhosis with ascites
3	A. R.	4322000000	2.22/2.97	....	227/..	Neg.	.....	.....	.....	Portal cirrhosis (autopsy)
4	H. J.	5553210000	3.74/2.29	0.24	150/55	Neg.	Neg.	.....	Gal. tol.—2.5 Gm. Brom.—2 per cent Levulose tol.—normal	Portal cirrhosis (autopsy)
5	P. M.	5553210000	2.53/4.25	0.21	150/44	Neg.	Pos.	Icteric index 17	.....	Portal cirrhosis with ascites
6	A. T.	2552110000	2.80/3.25	0.39	123/33	4+	Pos.	Direct—negative Indirect—normal	.....	Portal cirrhosis with ascites
7	H. P.	1553210000	3.31/3.07	....	126/17	Neg.	Pos.	Icteric index 25	.....	Portal cirrhosis with ascites
8	J. F.	5555442100	4.46/3.95	0.58	133/38	4+	Pos.	Direct—negative Indirect—normal	Brom.—5 per cent	Portal cirrhosis with ascites
9	A. B.	5532100000	4.22/2.17	0.21	132/..	2+	.....	Indirect—normal	.....	Portal cirrhosis and syphilis
10	F. H.	4453210000	.....	....	208/122	Neg.	Pos.	Icteric index 8.3	.....	Portal cirrhosis
11	F. M.	5521100000	2.87/2.84	....	138/41	Neg.	Pos.	.....	.....	Portal cirrhosis
12	E. S.	5555321000	2.66/3.65	....	176/78	Neg.	Neg.	Indirect—normal	.....	Portal cirrhosis with ascites
13	V. S.	5543210000	.....	....	.....	2+	Pos.	Indirect—normal	.....	Portal cirrhosis with ascites
14	P. T.	5543100000	2.62/5.06	....	160/70	Neg.	Pos.	Indirect—normal	.....	Portal cirrhosis (autopsy)
15	M. K.	5553210000	3.96/2.53	....	167/too low to measure	Neg.	Pos.	Indirect—7.4 mg. per 100 cc. Icteric index 60	.....	Portal cirrhosis
16	B. B.	4322000000	3.01/2.88	....	167/41	Neg.	Pos.	Indirect—6.2 mg. per 100 cc. Icteric index 50	.....	Portal cirrhosis with ascites
17	J. H.	5542110000	2.97/4.55	....	140/56	Neg.	Pos.	Indirect—normal	.....	Portal cirrhosis
18	M. C.	5321000000	2.49/3.43	....	155/58	Neg.	Neg.	Indirect—normal	.....	Portal cirrhosis
19	A. W.	5453210000	4.12/2.45	....	357/285	Neg.	Pos.	Icteric index 16	Gal. tot.—2.1 Gm.	Portal cirrhosis with esophageal varices
20	P. R.	4533210000	4.02/3.32	....	154/47	Neg.	Pos.	Indirect—normal	.....	Portal cirrhosis
21	L. F.	4455531000	3.42/3.69	....	150/70	Neg.	Pos.	Indirect—1.0 mg. per 100 cc.	.....	Portal cirrhosis
22	A. W.	5453210000	.....	....	.....	Neg.	.....	.....	.....	Portal cirrhosis
23	P. C.	4421100000	4.15/1.35	....	155/77	Neg.	Pos.	.....	.....	Portal cirrhosis with esophageal varices

24	S. R.	2683100000	3.68/4.18	....	218/90	Neg.	.....	.....	.....	Portal cirrhosis, macrocytic anemia
25	C. W.	1533210000	2.54/3.10	....	156/47	Neg.	.....	.....	.....	Portal cirrhosis with ascites
26	W. W.	4542431000	3.75/3.28	....	162/48	Neg.	Pos.	Icteric index 53	.....	Portal cirrhosis with ascites
27	A. V.	5554321000	3.60/1.96	....	125/ 5.5	Neg.	Pos.	Indirect—0.85 mg. per 100 cc.	.....	Portal cirrhosis
28	J. B.	5555321000	3.03/4.03	0.30	155/63	4+	Pos.	.....	.....	Portal cirrhosis with ascites
29	P. C.	5555310000	5.09/3.67	....	120/too low to read	Neg.	.....	.....	.....	Portal cirrhosis
30	M. W.	5554321000	4.38/2.89	....	238/170	Neg.	Neg.	Indirect—normal	.....	Portal cirrhosis (biopsy)
31	L. F.	5553210000	4.76/2.52	0.27	151/60	Neg.	Neg.	Indirect—4 mg. per 100 cc.	Brom.—no ret. Gal. tol.—2.1 Gm. Benzoic acid—3.1 Gm.	Early cirrhosis of liver (biopsy), macrocytic anemia, splenomegaly
32	L. W.	4332100000	3.79/2.81	....	169/95	Neg.	Pos.	Indirect—normal	Brom.—12 per cent	Subcapsular cirrhosis (autopsy)
33	B. H.	5554210000	.....	....	.....	Neg.	.....	.....	.....	Cardiac cirrhosis; large, hard, pulsating liver; ascites
34	A. D.	4522100000	4.33/2.80	....	.....	Neg.	Neg.	.....	.....	Cardiac cirrhosis; large hard liver; cardiac failure
35	K. R.	5554210000	3.14/3.66	....	137/59	Neg.	Pos.	Indirect—normal	.....	Cardiac cirrhosis; large, hard, nodular liver with ascites
36	A. A.	5543210000	3.91/2.87	....	160/60	4+	Pos.	Indirect—normal	.....	Cardiac cirrhosis; tricuspid regurgitation; large, hard, nodular liver with ascites
37	F. L.	5321000000	.....	....	.....	Neg.	.....	.....	.....	Cardiac cirrhosis (autopsy)
38	A. S.	5543100000	3.93/3.02	0.37	147/52	Neg.	.....	Direct—neg. Indirect—normal	Gal. tol.—1.0 Gm. Brom.—20 per cent	Cardiac cirrhosis with ascites (biopsy)
39	I. B.	5555321000	3.61/2.96	....	120/40	Neg.	Pos.	.....	.....	Cardiac cirrhosis; tricuspid regurgitation; large, hard, nodular liver
40	M. S.	5555321000	.....	....	.....	Neg.	Pos.	.....	.....	Cardiac cirrhosis; tricuspid regurgitation; large, hard, nodular liver
41	D. L.	5543210000	4.16/2.70	....	100/53	Neg.	Pos.	Indirect—normal	.....	Cardiac cirrhosis; heart failure; large, hard liver with ascites
42	B. J.	5554320000	2.33/5.09	....	138/48	Neg.	Pos.	Indirect—1.1 mg. per 100 cc.	.....	Hemochromatosis with cirrhosis of the liver (autopsy)
43	J. P.	5542100000	2.49/3.80	0.23	121/ 5.4	Neg.	Pos.	Biphasic—5 mg. per 100 cc.	Gal. tot.—3.2 Gm.	Biliary cirrhosis (autopsy)
44	A. E.	5555310000	4.16/3.18	....	357/80	Neg.	Pos.	Icteric index 80	.....	Biliary cirrhosis
45	J. L.	0443210000	2.96/2.60	....	302/..	Neg.	Pos.	Icteric index 82	Gal. tol.—1.5 Gm.	Biliary cirrhosis (autopsy)
46	L. A.	1433100000	4.14/1.65	0.27	88/39	Neg.	Neg.	Icteric index 15	.....	Atrophic cirrhosis with esophageal varices

normal (40 to 70 per cent of the total plasma cholesterol) in 14 cases and decreased in 22 cases of extensive involvement of the liver; in 2 of the latter the amount of esters was too low to determine. Better results were obtained with the Takata-Ara test in this group of cases than in any other group in our study, for 28 of the 35 tests performed were positive.

Acute Parenchymatous Hepatic Disease.—Positive colloidal gold reactions were obtained in 13 of 14 cases of acute parenchymatous disease of the liver (table 2). The single negative reaction observed was in the case of a 30 year old man with the clinical diagnosis of catarrhal jaundice, whose symptoms were subsiding when the test was made (table 2, case 5). The plasma proteins were determined in 10 of the 14 cases in this group. The globulin was increased to an average of 3.16 Gm. per hundred cubic centimeters. It is interesting that there were 6 cases with increased globulin, and that the average globulin values in acute parenchymatous disease of the liver and those in hepatic cirrhosis approximated each other closely. However, in contrast to the low albumin values found in hepatic cirrhosis, the albumin values in the parenchymatous diseases maintained a normal average of 4.38 Gm. and were abnormally low in only 2 instances. Total plasma proteins were normal in every case, with an average of 7.54 Gm., and were consistently higher than in the cases of cirrhosis of the liver. Positive colloidal gold reactions were again obtained in the presence of both abnormal and normal albumin globulin ratios—4 cases of the former and 6 of the latter.

The changes in the plasma cholesterol and cholesterol esters in this group were somewhat similar to those found in the cases of hepatic cirrhosis. The total plasma cholesterol was determined in 13 of the 14 cases and was found normal in 6, increased in 5 and decreased in 2. The plasma cholesterol esters, determined in 12 cases, were normal in 3 and decreased in 9; in 2 of these the quantity was too small to determine. The Takata-Ara reaction was considerably less sensitive than in the first group of cases, with only 3 positive tests among the 8 carried out.

Neoplastic Involvement of the Liver.—There were 25 cases of neoplastic disease of the liver, in which the diagnosis was confirmed in 13 instances by autopsy, biopsy or laparotomy. Positive colloidal gold reactions were obtained in 19 (table 3). In 4 of the 6 cases in which the reaction was negative there was minimal hepatic involvement, a few small carcinomatous nodules being found at autopsy. The plasma globulin, which averaged 3.10 Gm. per hundred cubic centimeters, was increased in 9 cases, whereas the plasma albumin averaged 3.73 Gm. and was decreased in 10 of the 17 cases studied. Since the increase in globulin compensated for the decrease in albumin, the total plasma

TABLE 2.—*Data on the Blood in Acute Parenchymatous Disease of the Liver*

Case No.	Patient	Serum Colloidal Gold Reaction	Plasma Albumin/ Globulin, Gm. per 100 Cc.	Plasma Cholesterol/ Cholesterol Esters, Mg. per 100 Cc.	Takata-Ara Test	Van den Bergh Reaction and Icteric Index	Galactose Tolerance, Bromsulphalein Retention and Other Tests	Diagnosis
1	R. S.	5543110000	4.68/2.53	185/67	Neg.	Icteric index 40	Gal. tol.—5.6 Gm.	Catarrhal jaundice
2	P. C.	5543210000	5.81/2.90	232/50	Pos.	Icteric index 83	Gal. tol.—4.4 Gm.	Catarrhal jaundice
3	F. I.	5553210000	4.47/2.22	333/125	Neg.	Icteric index 46	.....	Catarrhal jaundice
4	M. H.	5532110000	.....	154/33.6	Pos.	Icteric index 30	.....	Catarrhal jaundice
5	F. W.	0211000000	.....	.....	.....	.....	.....	Catarrhal jaundice
6	F. G.	5554000000	.....	131/..	.....	Icteric index 37	.....	Catarrhal jaundice
7	L. K.	5542210000	.....	181/too low to measure	Pos.	Direct—strong biphasic	.....	Catarrhal jaundice
						Indirect—4 mg. per 100 cc.	.....	Catarrhal jaundice
8	F. B.	5532100000	4.23/3.19	177/92	.....	Indirect—10 mg. per 100 cc.	Brom.—10 per cent	Infectious hepatitis (autopsy)
9	F. P.	5555421000	3.74/3.75	161/63	.....	Icteric index 75	.....	Toxic hepatitis with jaundice following pneumonia
		2332110000	4.37/2.01	.....	.....	Icteric index 15	.....	Six weeks later, no symptoms
10	R. S.	4432110000	4.19/2.84	212/87	.....	Icteric index 60	Gal. tol.—3.0 Gm.	Arsenical hepatitis
11	A. P.	4543100000	3.97/5.06	201/41.2	Neg.	Icteric index 65	Gal. tol.—6.4 Gm.	Arsenical hepatitis
12	L. B.	4533210000	4.33/3.35	241/65	Neg.	Icteric index 50	.....	Arsenical hepatitis
13	P. V.	4444310000	5.16/1.87	238/90	Neg.	Icteric index 49	Benzoic acid—1.62 Gm.	Cinchophen poisoning of liver
14	A. N.	5555431000	3.28/5.04	119/not readable	.....	Direct—immediate; indirect—10 mg. per 100 cc.	.....	Infectious hepatitis (autopsy)

TABLE 3.—*Data on the Blood in Neoplastic Diseases of the Liver*

Case No.	Patient	Serum Colloidal Gold Reaction	Plasma Albumin/ Globulin, Gm. per 100 Cc.	Plasma Fibrinogen, Gm. per 100 Cc.	Plasma Cholesterol/ Cholesterol Esters, Mg. per 100 Cc.	Takata-Ara Test	Van den Bergh Reaction and Icteric Index	Primary Source of Tumor
1	L. M.	4432110000	3.59/2.44	0.31	140/49	Neg.	Indirect—normal	Carcinoma of stomach with metastases to liver (laparotomy)
2	S. U.	4555320000	4.50/2.72	....	172/70	.....	.....	Carcinoma of stomach with metastases to liver (laparotomy)
3	P. M.	0233210000	4.24/2.49	....	127/63	Neg.	Indirect—normal	Carcinoma of stomach with a few small metastatic nodules in liver (laparotomy)
4	F. F.	5532110000	.....	....	.....	.....	.....	Carcinoma of stomach with metastases to liver (autopsy)
5	P. R.	0000100000	3.49/2.62	....	136/62	.....	.....	Carcinoma of stomach with metastases to liver (laparotomy); bromsulph. test normal
6	J. S.	1543210000	5.52/2.86	....	212/58	Neg.	Icteric index 99	Carcinoma of stomach with metastases to liver
7	B. K.	5543210000	1.76/4.73	....	58/not readable	Neg.	Direct—positive; indirect—4.7 mg. per 100 cc.	Carcinoma of stomach with metastases to liver (autopsy)
8	C. R.	0253310000	.....	....	.....	.....	.....	Carcinoma of breast with metastases to liver (autopsy)
9	E. S.	5553210000	.....	....	.....	Pos.	Indirect—normal	Carcinoma of breast with metastases to liver
10	M. J.	5321000000	4.26/2.44	....	139/38	Neg.	Indirect—4.6 mg. per 100 cc.	Carcinoma of breast with metastases to liver
11	N. S.	0042210000	.....	....	.....	Neg.	.....	Primary carcinoma of liver (biopsy)
12	A. M.	0454321000	3.55/3.07	0.6	185/73	Neg.	Indirect—normal	Primary tumor of liver (autopsy)
13	I. D.	5532100000	.....	....	.....	.....	.....	Carcinoma of prostate with metastases to liver, and ascites
14	P. P.	5555321000	2.56/3.98	....	160/40	.....	.....	Carcinoma of prostate with metastases to liver, and ascites
15	C. P.	1155321000	.....	....	.....	Neg.	Indirect—normal	Carcinoma of rectum with metastases to liver, and ascites
16	D. L.	5553210000	3.94/2.71	0.87	239/98	.....	Indirect—normal	Carcinoma of prostate with metastases to liver (biopsy)
17	H. A.	5555431000	6.20/3.50	....	118/42	Pos.	Indirect—normal	Carcinomatosis with involvement of liver
18	J. W.	5532100000	.....	....	.....	Neg.	.....	Carcinoma of pancreas with metastases to liver
19	A. K.	0211100000	2.21/3.25	....	.....	.....	Indirect—5.4 mg. per 100 cc.	Carcinoma of biliary tract with small amount of infiltration at hilus of liver (autopsy)
20	S. H.	1333210000	.....	....	.....	.....	Direct—biphasic; indirect—8.5 mg. per 100 cc.	Carcinoma of pancreas with a few small nodules in liver (autopsy)
21	A. V.	2332210000	3.31/3.53	1.35	111/32	.....	.....	Carcinoma of pancreas with metastases to liver
22	B. O.	0123211000	4.56/1.49	....	212/46	.....	.....	Carcinoma of pancreas extending up into hilus of liver (laparotomy); gal. tol., 5.8 Gm.
23	J. L.	4543210000	3.50/4.31	....	180/54	Neg.	Icteric index 60	Carcinoma of rectum with metastases to liver
24	F. P.	5533211000	2.06/3.48	0.25	141/44	.....	Indirect—normal	Carcinoma of rectum with metastases to liver
25	P. G.	0532210000	4.19/3.15	....	227/44	.....	Biphasic—strong; indirect—8.3 mg. per 100 cc.	Carcinoma of rectum with metastases to liver; gal. tol., 5.7 Gm.

proteins averaged 6.83 Gm. per hundred cubic centimeters, and were normal in 14 of the 17 cases studied. The degree of abnormality in the value for plasma protein was directly related to the extent and duration of the neoplastic involvement (table 3, cases 7, 14 23, 24). As in the other groups of cases, positive colloidal gold reactions did not occur only with abnormal plasma protein values, but were found in conjunction with normal globulin values in 5 instances and with normal albumin-globulin ratios in 4 instances.

The total cholesterol and the cholesterol esters of the plasma were determined in 16 of the 25 cases. The former was normal in 7 cases, high in 4 and low in 5 whereas the latter were normal in 5 cases and low in 11 cases of advanced parenchymal damage. The Takata-Ara test was less sensitive here than in the previous group of cases, yielding only 2 positive reactions in the 12 tests performed.

Miscellaneous Hepatic Diseases.—The colloidal gold reaction was positive in each of the 11 cases of miscellaneous hepatic diseases, in which the diagnosis was confirmed by autopsy or laparotomy in 8 cases (table 4). The plasma proteins were studied in 9 of the 11 cases. The globulin, averaging 2.99 Gm. per hundred cubic centimeters, was increased in 5 cases. Although the globulin values were less altered in this group than in the cases of other types of hepatic disease studied, the plasma albumin, averaging 3.27 Gm., was sufficiently low to produce abnormal albumin-globulin ratios in 8 of the 9 cases studied. The total plasma proteins, however, averaged 6.26 Gm. and were within the lower limits of normal in 6 of the 9 cases studied. Here again the colloidal gold reaction was positive in the 4 cases with normal plasma globulin values and in the 1 case with a normal albumin-globulin ratio.

The plasma cholesterol, determined in 9 cases, was normal in 5, high in 2 and low in 2, whereas the cholesterol esters, studied in 7 cases, were normal in 2 and low in 5. In 2 of these cases the values for the cholesterol esters were too low to determine. The Takata-Ara reaction was positive in 1 of the 3 tests performed.

The Colloidal Gold Reaction of Serum from Normal Persons and from Patients with Various Extrahepatic Diseases.—The colloidal gold reaction was studied in a control series of 95 nonsyphilitic persons with no demonstrable disease of the liver. This series included 20 normal adults and 75 patients with extrahepatic diseases, including lobar pneumonia, acute infectious diseases, acute and chronic nephritis, extrahepatic jaundice, blood dyscrasias and neoplasms. The presence of a normal liver was confirmed in 22 of the 75 cases at autopsy, biopsy or laparotomy. The colloidal gold reaction was negative in the serums from the 20 normal adults and in those of 73 of the 75 patients with various extrahepatic diseases. The 2 positive reactions were observed

TABLE 4.—*Data on the Blood in Miscellaneous Diseases of the Liver*

Case No.	Patient	Serum Colloidal Gold Reaction	Plasma Albumin/ Globulin, Gm. per 100 Cc.	Plasma Fibrinogen, Gm. per 100 Cc.	Plasma Cholesterol/ Cholesterol Esters, Mg. per 100 Cc.	Takata-Ara Test	Van den Bergh and Icteric Index	Galactose Tolerance, Bromsulphalein Retention and Other Tests	Diagnosis
1	O. Y.	5555221000	4.98/2.41	....	258/143	Pos.	Icteric index 62	.....	Chronic cholecystitis with hepatitis (laparotomy)
2	A. H.	4543210000	2.06/2.40	0.55	106/too low to measure	.....	.....	Brom.—20 per cent	Abscesses of liver (laparotomy)
3	R. C.	2433210000	3.31/3.20	....	176/65	.....	.....	.....	Hodgkin's disease—infiltration of liver (autopsy)
4	B. H.	4532100000	1.93/2.40	....	.....	.....	....	.....	Extreme degree of fatty degeneration of liver (autopsy)
5	E. K.	5521000000	3.05/2.38	....	120/too low to measure	.....	Indirect—10 mg. per 100 cc.	.....	Considerable fatty degeneration of liver (autopsy)
6	C. D.	5555421000	2.73/3.68	....	139/..	.....	.....	.....	Considerable fatty degeneration of liver (autopsy)
7	B. K.	1531000000	3.69/3.01	....	180/60	.....	.....	.....	Marked fatty degeneration of liver (autopsy)
8	G. B.	4522110000	.....	....	.....	Neg.	.....	Gal. tol.—2.7 Gm.; brom.—no ret.	Fatty infiltration of liver following diabetes (large, hard, smooth liver)
9	S. K.	5532110000	4.33/3.33	....	160/58	.....	.....	Gal. tol.—0.5 Gm.; brom.—no ret.	Hepatosplenomegaly and anemia
10	B. L.	5553210000	3.42/4.12	0.65	169/67	.....	.....	Brom.—3 per cent; benzoic acid—2.1 Gm.	Miliary infectious granuloma of liver (autopsy)
11	W. W.	5422210000	.....	....	376/..	Neg.	.....	Gal. tol.—2 Gm.	Lipoid histiocytosis (large hard liver)

TABLE 5.—*Data on Blood in Various Extrahepatic Diseases*

Case No.	Patient	Serum Colloidal Gold Reaction	Plasma Albumin/ Globulin Gm. per 100 Cc.	Plasma Cholesterol/ Cholesterol Esters, Mg. per 100 Cc.	Icteric Index	Diagnosis
1	J. O.	0001200000	.....	212/46	28	Common duct stone; liver normal (laparotomy)
2	G. W.	0123100000	5.57/3.14	313/163	125	Common duct stone; liver normal at operation
3	E. B.	0210000000	4.36/2.82	208/49	75	Common duct stone; liver normal at operation
4	L. M.	0110000000	5.05/2.89	170/71	...	Cholelithiasis; liver normal at operation
5	C. A.	0121000000	4.75/2.26	.....	115	Common duct stone; liver normal at operation
6	F. S.	0001000000	3.96/2.53	202/87	30	Common duct stone; liver normal at operation
7	T. H.	0013210000	4.11/2.86	193/60	41	Cholelithiasis; liver normal at operation
8	N. P.	0211000000	1.90/2.62	.....	...	Nephrotic nephritis
9	A. B.	2221000000	1.19/2.73	444/250	...	Nephrotic nephritis
10	A. M.	0111100000	4.54/1.72	155/60	...	Acute nephritis
11	D. H.	1211000000	1.63/3.31	.....	...	Chronic glomerulonephritis
12	A. L.	0000000000	2.90/3.87	.....	...	Chronic glomerulonephritis; liver normal at autopsy
13	S. K.	1121000000	4.01/3.33	175/86	...	Chronic glomerulonephritis
14	A. S.	2221000000	.....	.....	...	Chronic glomerulonephritis
15	F. G.	0111100000	4.75/3.14	174/90	...	Chronic glomerulonephritis; liver normal at autopsy
16	E. F.	2321000000	3.20/1.89	.....	...	Chronic glomerulonephritis; liver normal at autopsy
17	N. G.	1111000000	1.32/2.59	265/118	...	Chronic glomerulonephritis; liver normal at autopsy
18	A. M.	0110000000	3.80/2.72	176/29	...	Hodgkin's disease; liver normal at autopsy
19	B. G.	0111100000	4.29/1.96	135/54	...	Hodgkin's disease
20	K. R.	0110000000	4.22/1.81	.....	...	Lymphosarcoma (liver normal at autopsy)
21	G. S.	0110000000	.....	.....	...	Carcinoma of stomach; pneumonia; liver normal at autopsy
22	J. T.	2200000000	3.82/2.52	192/81	...	Carcinoma of stomach; liver normal at autopsy
23	A. L.	0022100000	3.54/3.12	171/51	...	Kidney tumor; liver normal at autopsy
24	B. C.	1122210000	3.98/3.58	.....	...	Carcinoma of lung
25	W. D.	0122100000	4.84/2.89	177/51	55	Carcinoma of biliary tract; liver normal at operation
26	A. B.	5554310000	3.41/3.53	129/64	...	Subacute bacterial endocarditis
27	C. J.	2221000000	4.48/3.05	.....	...	Subacute bacterial endocarditis
28	A. S.	0001200000	3.86/3.06	184/83	...	Coronary occlusion
29	A. H.	5553210000	2.89/3.34	182/102	...	Passive congestion of liver from cardiac failure (autopsy)
30	B. T.	0120000000	4.56/2.46	178/29	...	Rheumatic heart disease
31	S. S.	0111100000	2.96/3.46	160/30	...	Erysipelas
32	O. E.	0121100000	4.02/3.61	134/53	...	Acute sinusitis
33	S. L.	1232100000	.....	.....	...	Mastoiditis; temperature 104 F.; liver normal at autopsy
34	A. F.	0110000000	.....	.....	...	Pulmonary tuberculosis; liver normal at autopsy
35	S. W.	0121100000	5.43/1.28	159/67	...	Pulmonary tuberculosis; liver normal at autopsy
36	A. L.	0110000000	4.66/2.34	.....	...	Pernicious anemia
37	B. G.	0221000000	4.87/2.28	141/56	...	Pernicious anemia
38	S. R.	0210000000	5.45/2.04	.....	...	Duodenal ulcer
39	P. N.	1123300000	2.98/4.02	206/108	...	Duodenal ulcer
40	R. C.	0110000000	4.50/2.06	190/88	...	Spastic colitis
41	S. H.	1221100000	4.29/2.17	174/69	...	Bacillary dysentery
42	S. H.	0111000000	3.54/2.17	128/49	...	Hyperthyroidism
43	L. G.	1100000000	5.16/1.88	143/62	...	Splenomegaly; liver normal (biopsy)
44	S. H.	0121000000	4.87/2.88	187/98	...	Boeck's sarcoid
45	G. A.	0111000000	4.35/2/21	.....	...	Multiple myeloma

in a case of subacute bacterial endocarditis and in one of passive congestion of the liver. Data on 45 of the cases of extrahepatic disease are given in table 5.

The values for plasma albumin, globulin, cholesterol and cholesterol esters were found to be within normal limits in the 20 normal adults. Plasma protein determinations in 40 of the 75 cases of extrahepatic disease revealed a normal average value for globulin of 2.70 Gm. per hundred cubic centimeters, and a slightly lowered value for albumin, 3.96 Gm. Normal total proteins, averaging 6.66 Gm. per hundred cubic centimeters, were present in 35 of the 40 cases. The albumin was diminished in 16 cases; it was markedly decreased in 3 cases of acute

TABLE 6.—*Data on Blood Serum in Syphilis*

Case No.	Patient	Serum Colloidal Gold Reaction	Plasma Albumin/ Globulin Gm. per 100 Cc.	Plasma Cholesterol/ Cholesterol Esters, Mg. per 100 Cc.	Wassermann Reaction	Diagnosis
1	F. M.	1221100000	4.07/2.17	156/76	3+	Central nervous system syphilis; no arsenical therapy
2	F. K.	5442110000	3.69/3.46	162/42	4+	Central nervous system syphilis; arsenical therapy
3	A. S.	5555321000	4.76/2.89	134/58	4+	Central nervous system syphilis; arsenical therapy
4	L. S.	2532110000	3.68/3.44	159/60	4+	Syphilitic heart disease; arsenical therapy
5	T. M.	5521110000	4.17/3.13	.....	4+	Syphilitic heart disease; no arsenical therapy
6	B. S.	1532100000	.....	.....	...	Syphilitic heart disease; no arsenical therapy
7	N. M.	5552100000	4.85/3.14	175/90	3+	Primary syphilis; mild hepatitis from arsenical therapy
8	S. L.	5321000000	.....	.....	...	Primary syphilis; arsenical therapy
9	L. F.	1221000000	.....	.....	...	Secondary syphilis; arsenical therapy
10	F. M.	5521000000	.....	.....	...	Secondary syphilis; arsenical therapy
11	N. D.	0231000000	3.71/4.02	127/44	4+	Tertiary syphilis; splenomegaly; liver normal size

nephritis and 3 of chronic nephritis with albuminuria, and was lowered to a lesser degree in 2 cases of heart disease (in 1 of which ascites was present), 2 of infectious diseases, 4 of neoplasm, 1 of hyperthyroidism and 1 of duodenal ulcer. An increase in the plasma globulin was observed in 15 of the 16 cases in which the plasma albumin was decreased. The colloidal gold reaction was negative in 13 of the 15 cases with high globulin values.

The plasma cholesterol was elevated in 4 cases of extrahepatic jaundice and normal in 2, in contrast to the cholesterol values in intrahepatic jaundice, relatively few of which were above normal. The cholesterol esters were normal in 3 cases of jaundice and lowered in 3. In 24 cases of extrahepatic disease without jaundice, the cholesterol was normal in 18, high in 3 and low in 3, whereas the cholesterol esters were normal in 18 cases and lowered in only 6, in contrast to the predominant lowering observed in intrahepatic disease.

Serum Colloidal Gold Reaction in Syphilis.—The colloidal gold reaction was positive in 8 and negative in 12 of 20 cases of syphilis with no clinical evidence of hepatic involvement. Data for 11 of these cases are given in table 6. The plasma globulin, averaging 3.17 Gm. per hundred cubic centimeters, was increased in 5 of the 7 cases in which proteins were determined, and the colloidal gold reaction was positive

TABLE 7.—*Comparison of Colloidal Gold Reaction of Blood Serum and of Spinal Fluid*

	Colloidal Gold Reaction		Wassermann Reaction		Globulin in	
Case No.	Blood Serum	Cerebrospinal Fluid	Blood	Spinal Fluid	Cerebrospinal Fluid	Diagnosis
1	1221100000	4443331000	3+	4+	++	Cerebrospinal syphilis
2	5442110000	5555321000	4+	4+	++	Cerebrospinal syphilis
3	5555321000	5555321000	4+	4+	+	Cerebrospinal syphilis
4	4553210000	4553200000	4+	Neg.	+	Cerebrospsinal syphilis
5	2321000000	5555321000	4+	4+	.....	Cerebrospinal syphilis
6	1230000000	2223331110	4+	4+	++	Cerebrospinal syphilis
7	2221000000	5531000000	4+	Neg.	Neg.	Cerebrospinal syphilis
8	1210000000	5554321000	4+	4+	.....	Cerebrospinal syphilis
9	5555310000	5555432100	4+	4+	++	Cerebrospinal syphilis and cirrhosis of liver
10	2532110000	0011000000	4+	Neg.	.....	Syphilitic heart disease; large, hard smooth liver
11	1253110000	0000110000	3+	Neg.	Neg.	Syphilitic heart disease; large, hard liver
12	5321110000	1112000000	4+	4+	.....	Syphilitic heart disease; large hard liver
13	5532100000	0012000000	3+	Neg.	+	Secondary syphilis; history of toxic hepatitis
14	5532100000	0000100000	2+	Neg.	Neg.	Primary syphilis and arsenical hepatitis
15	1221000000	0000000000	4+	Neg.	Neg.	Primary syphilis
16	0220000000	0000000000	4+	Neg.	Neg.	Primary syphilis
17	2210000000	0010000000	3+	.....	.....	Primary syphilis
18	0232110000	0000110000	4+	.....	.....	Primary syphilis
19	0122100000	4441113321	Neg.	Neg.	+++	Meningococcic meningitis
20	0122100000	0000210000	Neg.	Neg.	Neg.	Biliary tract neoplasm; liver normal (autopsy)
21	2221000000	0011000000	Neg.	Neg.	.....	Parkinsonism
22	0110000000	0001210000	Neg.	Neg.	+	Miliary tuberculosis; liver normal (autopsy)
23	1232100000	0011000000	Neg.	Neg.	+	Epidural abscess; liver normal (autopsy)
24	0454321000	0010000000	Neg.	Neg.	.....	Primary tumor of liver (autopsy)
25	5544531000	0012100000	Neg.	Neg.	.....	Portal cirrhosis of liver

in 4 of the 5 cases. The albumin was reduced in 3 of the 7 cases, but the average value was normal—4.13 Gm. In the 6 cases in which the plasma cholesterol and cholesterol esters were determined, the former was normal in 4 and low in 2 while the latter were normal in 3 and low in 3.

Comparison of the Colloidal Gold Reaction in the Blood Serum and in the Cerebrospinal Fluid.—The colloidal gold reaction of the spinal fluid and that of the blood serum from the same patient may be the same or may differ greatly, depending on the disease process (table 7). The colloidal gold reaction was positive in the blood serum and negative in the spinal fluid of 7 patients with liver disease. This

group included 3 patients with syphilitic heart disease and large, hard livers (table 7, cases 10, 11, 12), 1 patient with portal cirrhosis (case 25), 2 with arsenical hepatitis (cases 13 and 14) and 1 with a hepatic tumor (case 24). In 4 cases of cerebrospinal syphilis, colloidal gold reactions were positive in the spinal fluid and negative in the blood serum, with increased globulin in the spinal fluid in 1 instance (cases 1, 5, 7, 8). On the other hand, in 3 similar cases the colloidal gold reactions in both the spinal fluid and the blood serum were positive, with increased globulin in the spinal fluid in 3 instances (table 7, cases 2, 3, 4). In 1 case (case 9), in which both syphilis of the central nervous system and hepatic cirrhosis were present, both the spinal fluid and the blood serum gave positive reactions. In 3 cases of early syphilis with no evidence of hepatic disease (cases 16, 17, 18) and in 3 cases of various conditions other than hepatic disease or syphilis (cases 21, 22, 23) there were negative colloidal gold reactions in both the spinal fluid and the blood serum. The spinal fluid globulin was increased in 2 of these cases. In 1 case (case 19) of meningococcic meningitis, with no clinically detectable hepatic disease, a positive colloidal gold reaction was obtained in the spinal fluid and a negative reaction in the blood serum.

COMMENT

In these studies there was a high incidence of positive colloidal gold reactions in the blood serums of patients with hepatic disease. The reactions were positive in 89 of the 96 cases of hepatic disease studied (92.7 per cent). Positive reactions were obtained in every case of cirrhosis of the liver, in all but a single case of acute parenchymatous disease of the liver and in all the cases of miscellaneous hepatic disease studied. The reaction was negative in a case of mild catarrhal jaundice with subsiding symptoms and in 6 cases of neoplastic disease of the liver, in 4 of which autopsy revealed minimal involvement or a few small malignant nodules.

The sensitivity of the colloidal gold reaction was of considerable clinical importance in several cases of hepatic disease, confirmed by autopsy or biopsy in 4 instances, in which bilirubin excretion, bromsulphalein retention and other tests were negative. In 1 of these cases (L. F. [table 1, case 31, a 47 year old woman with splenomegaly, macrocytic hyperchromic anemia, jaundice, reticulocytosis and normal blood fragility]), the colloidal gold reaction in the serum was repeatedly positive. Various tests, including the bromsulphalein retention, bilirubin excretion, hippuric acid, galactose tolerance, levulose tolerance and Takata-Ara tests, gave normal results. A small, firm, diffusely nodular cirrhotic liver was found at operation. Similarly, normal results were

obtained with one or more of the foregoing tests made in 3 cases of hepatic disease in which the diagnoses of portal cirrhosis, primary tumor of the liver and miliary infectious granuloma of the liver were confirmed at autopsy (table 1, case 4; table 3, case 12; table 4, case 10). The colloidal gold reaction, however, was persistently positive in all 3 cases. It is interesting to note that the bromsulphalein retention test in the 12 cases of hepatic disease in which it was used was positive in 6 cases and negative in 6, while the colloidal gold reaction was positive in 11 of the 12 cases.

While these studies were being completed Bauer [17] reported somewhat similar observations on the colloidal gold reaction and compared his results with the Takata-Ara test. In my studies I found the Takata-Ara test less sensitive than the colloidal gold test. It was positive in 28 of 35 cases of hepatic cirrhosis, in 3 of 8 cases of acute parenchymatous liver disease, in 2 of 12 cases of neoplastic hepatic involvement and in 1 of 3 cases of miscellaneous hepatic disease, a total of 34 positive tests in 58 cases (58.6 per cent).

In cases of extrahepatic jaundice of short duration (such as that resulting from a stone in the common duct) in which the liver was found to be normal at operation, the colloidal gold reactions were negative regardless of the degree of jaundice (table 5, cases 1, 2, 3, 5, 6, 7). The amount of serum bilirubin present did not appear to alter the reaction. In cases of extrahepatic jaundice of long duration, however, with secondary liver involvement found at operation, the colloidal gold reaction was positive (table 4, case 1).

The reaction was negative in other diseases in which there was no clinically detectable pathologic change in the liver, as in acute and chronic nephritis, infectious diseases, neoplastic diseases and blood dyscrasias. The diagnosis of a normal liver was confirmed by autopsy, biopsy or laparotomy in 22 cases. In a case of lobar pneumonia (table 2, case 9) jaundice developed; the colloidal gold reaction was positive until the symptoms of hepatitis had subsided. Positive reactions were obtained in a case of subacute bacterial endocarditis and in one of passive congestion of the liver.

Observations of the colloidal gold reaction in syphilis indicate a high percentage of disease of the liver following antisyphilitic therapy (table 6). Five of the 8 positive colloidal gold reactions were in cases with histories of previous arsenical therapy; in 1 of these there had been hepatitis (table 6, case 7). However, 7 of the 12 negative reactions were found in cases with histories of similar arsenical therapy. Whether the positive reactions obtained in syphilitic serums represent subthreshold

17. Bauer, R.: Eine neue Seroreaktion—Serum Goldsolreaktion, Klin. Wchnschr. **16**:1570, 1937.

hepatic disease following arsenical therapy [18] or whether they represent false positive reactions, related in some way to the altered globulin content apparently present in syphilis,[19] cannot be concluded at this time.

The differences between the colloidal gold reaction of the blood serum and that of the spinal fluid in various diseases may be explained by the blood-brain barrier's acting as a semipermeable membrane which excludes such proteins as euglobulin and fibrinogen from the spinal fluid.[20] This permeability is altered in various pathologic conditions of the meninges, such as cerebrospinal syphilis and meningococcic meningitis.[21]

The studies of the plasma cholesterol esters are interesting in that they demonstrate the rather high incidence (66.2 per cent) of abnormal values in hepatic disease.[22] Decreases in the cholesterol esters were

18. (*a*) O'Leary, P. A.; Snell, A. M., and Bannick, E. G.: Portal Cirrhosis Associated with Chronic Inorganic Arsenical Poisoning: Report of Two Cases, J. A. M. A. **90**:1856 (June 9) 1928. (*b*) O'Leary, P. A.: Observations on the Treatment of Syphilis of the Liver, ibid. **96**:183 (Jan. 17) 1931. (*c*) Baldridge, C. W.: The Relationship Between Antisyphilitic Treatment and Toxic Cirrhosis, Am. J. M. Sc. **188**:685, 1934. (*d*) Biskind, G. R.; Epstein, N. N., and Kerr, W. J.: Hepatic Complications in the Treatment of Syphilis, Ann. Int. Med. **7**:966, 1934. (*e*) Kellogg, F.; Epstein, N. N., and Kerr, W. J.: Hepatic Complications in the Treatment of Syphilis, ibid. **9**:1561, 1936. (*f*) Sager, R. V.: Factors Responsible for Jaundice in Syphilis, with Special Reference to the Role of the Arsphenamines, Arch. Int. Med. **57**:666 (April) 1936.

19. (*a*) Noguchi, H.: The Relation of Protein, Lipoids and Salts to the Wassermann Reaction, J. Exper. Med. **11**:84, 1909. (*b*) Winternitz, R.: Ein Beitrag zur chemischen Untersuchung des Blutes rezent luetischer Menschen, Arch. f. Dermat. u. Syph. **93**:65, 1908. (*c*) Müller, R., and Hough, W. H.: Vergleichende Globulinmessungen an luetischen Seris, Wien. klin. Wchnschr. **24**:167, 1911. (*d*) Takuda, K.: Refractometric Studies in Human Syphilis with Special Reference to Changes During Treatment with Arsphenamine and Neoarsphenamine, Arch. Dermat. & Syph. **4**:512 (Oct.) 1921. (*e*) Bircher, M. A., and McFarland, A. R.: The Globulin Content of the Blood Serum in Syphilis, ibid. **5**:215 (Feb.) 1922. (*f*) Lloyd, R. B.: Protein Graphs in Syphilis with Their Relation to the Wassermann Reaction, Indian J. M. Research **19**:1055, 1932.

20. Greenfield, J. G., and Carmichael, E. A.: The Cerebrospinal Fluid in Clinical Diagnosis, New York, The Macmillan Company, 1925.

21. (*a*) Greenfield, J. G.: Some Modern Problems Connected with the Cerebrospinal Fluid, Edinburgh M. J. **43**:573, 1936. (*b*) Katzenelbogen, S.: The Cerebrospinal Fluid and Its Relation to the Blood, Baltimore, Johns Hopkins Press, 1935.

22. (*a*) Thannhauser, S. J., and Schaber, H.: Ueber die Beziehungen des Gleichgewichtes Cholesterin und Cholesterinester im Blut und Serum zur Leberfunktion, Klin. Wchnschr. **5**:252, 1926. (*b*) Adler, A., and Lemmel, H.: Zur feineren Diagnostik der Leberkrankheiten: I. Cholesterin und Cholesterinester im Blute Leberkranker, Arch. f. klin. Med. **158**:173, 1928. (*c*) Epstein, E. Z.:

(Footnote continued on next page)

observed in 47 of 71 cases of hepatic disease; in contrast, in the extrahepatic diseases the esters were decreased in 9 of the 30 cases. The incidence of low cholesterol esters in the various types of hepatic disease was approximately the same: 22 of 36 cases of cirrhosis (61.1 per cent), 9 of 12 cases of acute parenchymatous disease (75 per cent), 11 of 16 cases of neoplastic disease (68.8 per cent) and 5 of 7 cases of miscellaneous hepatic diseases (71.4 per cent). Extensive parenchymal damage was frequently associated with low cholesterol ester values (table 1, cases 27, 43; table 2, case 14; table 3, case 7). Changes in the cholesterol–cholesterol ester ratio paralleled the alteration of the plasma proteins except in the acute parenchymatous diseases, in which decreases in cholesterol esters were found more frequently than altered plasma protein values. The total plasma cholesterol values were not altered so readily, however; they were normal in 38, high in 18 and low in 21 of the 77 cases of hepatic disease studied. Normal values were observed in about half the cases of hepatic disease and in two thirds of the cases of extrahepatic diseases. An increase in plasma cholesterol was found in 4 of the 6 cases of extrahepatic jaundice, in contrast to the predominantly normal values observed in intrahepatic jaundice.

The poor prognosis associated with low cholesterol ester values [23] is demonstrated in 6 of the 7 cases in which the cholesterol esters were too low to determine. Death occurred in 6 cases within two months; 1 patient (table 2, case 7), with catarrhal jaundice, survived. In general, the decrease in cholesterol esters paralleled the severity of the hepatic injury; the cholesterol esters were frequently normal in the early stages of mild hepatic disease.

Variations in the plasma proteins were encountered frequently in 75 cases of hepatic disease in which protein values were determined. The globulin was increased in 43 cases and the albumin decreased in 45. The increase in globulin usually compensated for the decrease in albumin, so that the total plasma proteins were normal in all but 15 cases. It is interesting to observe that the lowest ratios—that is, the greatest increases in globulin and decreases in albumin—were associated with advanced hepatic destruction (table 1, case 14; table 2, case 14; table 3, case 7). The most marked variations in albumin and globulin values were found in cirrhosis of the liver, and the least marked variations were noted in the acute parenchymatous diseases.

The Cholesterol Partition of the Blood Plasma in Parenchymatous Diseases of the Liver, Arch. Int. Med. **47**:82 (Jan.) 1931; Cholesterol of the Blood Plasma in Hepatic and Biliary Diseases, ibid. **50**:203 (Aug.) 1932.

23. Adler and Lemmel.[22b] Epstein.[22c]

The changes in concentration of the plasma proteins were related more closely to the severity and duration of the disease of the liver than to the state of nutrition or to loss of protein in the ascitic fluid. Moderately advanced hepatic disease without demonstrable ascites (table 3, cases 7, 23, 24; table 1, cases 1, 17, 21, 24) may produce greater variation in protein concentrations than less advanced hepatic disease with ascites (table 1, cases 8, 16, 36). One patient with a large, hard, irregular liver, cardiac decompensation and ascites of long duration had normal plasma proteins (table 1, case 41). No definite correlation could be found between malnutrition or inadequate protein intake and altered plasma proteins. Myers and Keefer,[13f] Foley and associates [13g] and Snell and Magath [24] have shown that the shifts in plasma proteins so frequently observed in hepatic disease are caused primarily not by deficient intake of protein or mechanical loss in the ascitic fluid but by defective formation of proteins. Holman, Mahoney and Whipple,[25] Kerr, Hurwitz and Whipple,[26] Sawada [27] and others [28] have concluded that the liver plays an important role in maintaining normal serum proteins.

The positive colloidal gold reaction does not depend primarily on a quantitative increase in globulin, a decrease in albumin or an inversion of the albumin-globulin ratio. Positive reactions were present in 29 of the 32 cases with normal plasma globulin values and in 21 of the 23 cases with normal albumin-globulin ratios. Conversely, in the control series the colloidal gold reaction was negative in 13 of the 15 cases with elevated plasma globulin values and in each of the 15 cases with low or inverted albumin-globulin ratios. The positive colloidal gold reaction may depend, therefore, on a qualitative rather than on a quantitative alteration in the plasma proteins. The work of Gros,[14a] Kendall [14b] and de Vries [14c] indicates that the increased globulin found

24. Snell, A. M., and Magath, T. B.: The Use and Interpretation of Tests for Liver Function: A Clinical Review, J. A. M. A. **110**:167 (Jan. 15) 1938.

25. Holman, R. L.; Mahoney, E. B., and Whipple, G. H.: Blood Plasma Protein Given by Vein Utilized in Body Metabolism: II. A Dynamic Equilibrium Between Plasma and Tissue Proteins, J. Exper. Med. **59**:269, 1934.

26. Kerr, W. J.; Hurwitz, S. H., and Whipple, G. H.: Regeneration of Blood Serum Protein: III. Liver Injury Alone, Liver Injury and Plasma Depletion; the Eck Fistula Combined with Plasma Depletion, Am. J. Physiol. **47**: 379, 1918.

27. Sawada, T.: Biochemical Investigation of the Blood in Cases of Experimental Disturbance of Liver Function, Jap. J. Gastroenterol. **3**:38, 1931.

28. (*a*) Mann, F. C., and Magath, T. B.: Die Wirkungen der totalen Leberexstirpation, Ergebn. d. Physiol. **23**:212, 1924. (*b*) Salvesen, H. A.: Variations in the Plasma Protein in Non-Renal Conditions, Acta med. Scandinav. **72**:113, 1929. (*c*) Henriques, V., and Klausen, U.: Untersuchungen über den Serumalbumin und Serumglobulingehalt des Serums unter wechselden Umständen, Biochem. Ztschr. **254**:414, 1932.

in hepatic disease differs from that found in other diseases in that the euglobulin constitutes a higher percentage of the increase in globulin. It is suggested that since euglobulin is believed to play an important role in the colloidal gold precipitation [15] and is thought to be specifically increased in hepatic disease, it may be responsible for the positive reactions obtained. Further work on the globulin fractions is being done.

SUMMARY AND CONCLUSIONS

The colloidal gold reaction of the blood serum was studied in a series of 96 cases of hepatic disease, grouped as follows: 46 cases of cirrhosis, 14 cases of acute parenchymatous disease, 25 cases of neoplastic involvement and 11 cases of miscellaneous hepatic disease. The diagnoses were confirmed by autopsy, biopsy or laparotomy in 34 cases: 11 in the first group, 2 in the second, 13 in the third and 8 in the fourth. The reaction was positive in each of 46 cases of cirrhosis, in 13 of 14 cases of acute parenchymatous involvement, in 19 of 25 cases of neoplasm and in each of 11 cases of miscellaneous hepatic disease. In the entire series, the reaction was positive in 89 of the 96 cases, or 92.7 per cent.

In several instances the colloidal gold reaction detected liver disease, later confirmed by operation or autopsy, which had not been detected by the usual clinical and chemical tests.

The colloidal gold reaction was negative with serums from 20 normal adults and in 73 of 75 cases of various extrahepatic diseases; normal livers were found in 22 of these cases at autopsy, biopsy or laparotomy.

Positive reactions were obtained in 8 of 20 cases of syphilis; in 1 of these 8 cases there was a history of hepatitis but in the others there was no demonstrable hepatic disease. The possibility of latent damage to the liver following arsenical therapy and the question of false positive reactions in syphilis are discussed. It is pointed out that the colloidal gold reaction of the spinal fluid and that of the blood serum may be the same or may differ greatly, depending on the effects of disease processes on the permeability of the blood-brain barrier.

The Takata-Ara reaction was positive in only 34 of 58 cases of hepatic disease (58.6 per cent); it was thus considerably less sensitive than the colloidal gold reaction.

The total plasma cholesterol was normal in 38 of the 77 cases of hepatic disease studied.

However, decreased values for plasma cholesterol esters were frequently associated with extensive parenchymal damage and were present in 47 of 71 cases of hepatic disease (66.2 per cent). The decrease paralleled the severity of the hepatic injury and was of prognostic significance; 6 of the patients whose cholesterol esters were too low to determine died within two months.

Changes in the cholesterol–cholesterol ester ratio paralleled the shifts in the plasma proteins in all types of liver disease except the acute parenchymatous diseases, in which lowered cholesterol esters were more frequent than altered plasma protein values.

Variations in the plasma proteins were frequent in hepatic disease; globulin was increased in 43 cases, and albumin was decreased in 45 of the 75 cases studied. The increase in globulin was usually greater than the decrease in albumin, so that the total proteins were normal in 60 of the 75 cases.

The most marked albumin-globulin shifts occurred in cirrhosis of the liver and were associated with advanced hepatic destruction; the least marked variations were found in the acute parenchymatous hepatic diseases. The changes in concentration of the plasma proteins were related more closely to the severity and duration of the hepatic disease than to the state of nutrition or to the loss of protein associated with ascites.

The colloidal gold reaction does not depend primarily on a quantitative increase of globulin or on a low or inverted albumin-globulin ratio. Positive reactions were obtained in 29 cases of hepatic disease with normal plasma globulin values and in 21 cases with normal albumin-globulin ratios. The mechanism of the reaction is unknown. It is suggested that it may depend on a qualitative rather than on a quantitative variation in the plasma globulin and that the euglobulin may be an important factor in the reaction.

Drs. George F. Dick and Walter L. Palmer gave many suggestions during this study, and Miss Kathryn Knowlton and Miss Lois Seago gave technical assistance.

THE BRAIN IN MALIGNANT HYPERTENSION*

A CLINICOPATHOLOGIC STUDY

EDWARD F. ROSENBERG, M.D.
Fellow in Medicine, the Mayo Foundation
ROCHESTER, MINN.

As a result of the original concepts of Volhard and Fahr,[1] a malignant (*bösartig*) form of hypertension was separated from the general group in 1914. In 1924, however, Wagener and Keith [2] described a syndrome of malignant hypertension and showed that this condition deserves the distinction of an entity, differing from chronic glomerulitis and benign hypertension on the basis of age incidence, a characteristic retinal picture, absence of anemia and frequent persistence of adequate renal function. This clinical concept of Wagener and Keith was further developed in investigations at the Mayo Clinic, the results of which were published in 1927,[3] 1928,[4] 1929,[5] and 1931,[6] and various pathologic studies of this disease have been reported from this institution by Cain,[7] Morlock [8] and Odel.[9] None of these works included any compre-

From the Division of Medicine, Section of Pathologic Anatomy and Section of Ophthalmology, the Mayo Clinic.

* Objection has been raised to the use of the term malignant hypertension. In this paper, the term has been used interchangeably with diffuse arteriolar disease with hypertension, group 4.

1. Volhard, F., and Fahr, K. T.: Die Brightsche Nierenkrankheit: Klinik, Pathologie und Atlas, Berlin, Julius Springer, 1914.

2. Wagener, H. P., and Keith, N. M.: Cases of Marked Hypertension, Adequate Renal Function and Neuroretinitis, Arch. Int. Med. **34**:374-387 (Sept.) 1924.

3. Keith, N. M.: Classification of Hypertension and Clinical Differentiation of the Malignant Type, Am. Heart J. **2**:597-608 (Aug.) 1927.

4. Keith, N. M.; Wagener, H. P., and Kernohan, J. W.: The Syndrome of Malignant Hypertension, Arch. Int. Med. **41**:141-188 (Feb.) 1928.

5. Kernohan, J. W.; Anderson, E. W., and Keith, N. M.: The Arterioles in Cases of Hypertension, Arch. Int. Med. **44**:395-423 (Sept.) 1929.

6. Keith, N. M.; Barker, N. W., and Kernohan, J. W.: Histologic Studies of the Arterioles in Various Types of Hypertension, Tr. A. Am. Physicians **46**: 66-70, 1931.

7. Cain, E. F.: Malignant Hypertension: The Histologic Changes in the Kidneys, Arch. Int. Med. **53**:832-850 (June) 1934.

8. Morlock, C. G.: Arterioles of the Pancreas, Liver, Gastrointestinal Tract, and Spleen in Hypertension, Arch. Int. Med. **63**:100-118 (Jan.) 1939.

(Footnote continued on next page)

hensive data regarding the brain. The purpose of the present study has been to survey the brain in cases of malignant hypertension, to catalogue the lesions present and, if possible, to correlate these lesions with symptoms that occurred in life.

When this study was in progress, the autopsy material at the Mayo Clinic included 17 brains of persons who had died of malignant hypertension. A review of the clinical data on the patients and the pathologic observations on the brains forms the basis of the present communication.

In the group of cases on which this study is based there were 5 women and 12 men, and this sex distribution agrees with the generally observed higher incidence of malignant hypertension among men. The diagnosis of malignant hypertension was based on the criteria of Keith, Wagener and Kernohan.[4] The age range for the group was from 7 to 65 years, the mean age being 43.

The duration of life after the onset of symptoms varied from four to eighteen months and averaged eight and nine-tenths months, thus again justifying the designation of this disease as "malignant." The symptoms in this group were predominantly referable to the central nervous system. This predominance was perhaps somewhat more marked than would be noted in a more general review of malignant hypertension; the difference may be explainable by the fact that special efforts are made to secure permission for examination of the brain when outstanding evidences of cerebral damage have been present during life. However, it should be stated that practically all patients with malignant hypertension have some clinical evidences of cerebral disturbances.

OBJECTIVE FINDINGS

The objective findings in patients with malignant hypertension have been thoroughly described by the authors whom I have already mentioned, and I need only review briefly the findings in this series of patients.

In all of these patients high blood pressure was present, and at times the systolic pressure exceeded 200 mm. of mercury; in some of them it exceeded 250 mm. The diastolic pressure often exceeded 120 mm. Figure 1 illustrates a characteristic course with regard to blood pressure in these patients. A distinctive retinal picture was always present during life; this was characterized by narrowing and sometimes by sclerosis of the retinal arteries, flame-shaped hemorrhages, cotton wool exudates and edema of the optic disks. Evidence of cardiac damage

9. Odel, H. M.: A Study of the Changes in the Arterioles of the Myocardium in a Group of Cases of Diffuse Arteriolar Disease with Hypertension, Group IV, Thesis, Minnesota University Graduate School, 1937; Arteriolar Changes in the Myocardium in Diffuse Arteriolar Disease with Hypertension, Group IV, abstracted, Proc. Staff Meet., Mayo Clin. **14**:210-214 (April 5) 1939.

was usually present, varying from simple enlargement of the heart, with accentuation of the aortic second sound, to advanced heart failure, with anasarca, orthopnea and cyanosis. Frequently when the patient was seen early renal function was good, and not uncommonly it was adequate even to the time of death. However, renal function often failed in the terminal stages.

Laboratory Data.—The urine often showed albumin. Cylindruria was present in some instances, as were erythrocytes. A study of the chemistry of the blood was made, particularly with reference to renal function. These studies showed that severe renal insufficiency preceded death in 12 instances. It is well to stress, however, that 5 patients were without severe renal failure until death. Thus, patients in this group of cases of malignant hypertension always had so-called retinitis albuminurica with papilledema and may or may not have had renal insufficiency.

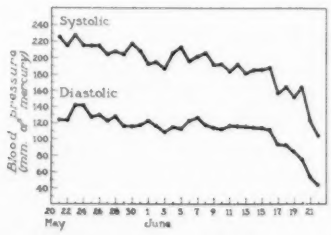


Fig. 1 (case 14).—Blood pressure readings observed daily during final month of the terminal illness of the patient. Note how the high level of systolic and diastolic pressures was maintained until within a few days of death, despite gross clinical evidence of congestive heart failure during this period.

Anemia was present in 7 instances, but was severe in only 2.

Neurologic Examination.—In the absence of a definite history of cerebrovascular accident with hemiplegia, the results of the neurologic examination were objectively negative in all but 2 instances; in these Babinski phenomena were present during life. These 2 cases will be referred to later.

Cerebrospinal Fluid.—In 7 instances lumbar punctures were performed during life (table 1). It is interesting that in 5 of the 7 cases pressure of the subarachnoid fluid was elevated (28 to 35 cm. of water) at the time of the first examination, whereas in 2 cases the pressure was normal (8 and 16 cm. of water). Two patients who had elevated pressures on a single occasion had normal pressures on subsequent studies.

Thus, one cannot conclude that edema of the optic disks in a patient with malignant hypertension always denotes increased pressure of the

cerebrospinal fluid, although usually these two conditions are associated. Factors such as occlusion of the foramen occipitale magnum by the brain stem may prevent one's obtaining a true reading of the intracranial subarachnoid pressure by lumbar puncture.

The behavior of the cerebrospinal fluid in essential hypertension has been carefully studied in recent years. Admirable reports have been published by Shelburne, Blaine and O'Hare [10] in the United States and

TABLE 1.—*Correlation of Clinical Findings with the Presence of Edema of the Brain in Cases of Malignant Hypertension*

Case	Pressure of Cerebrospinal Fluid, Cm. of Water	Choking of Disks, Diopters		Last Concentration of Urea, Mg. per 100 Cc. of Blood	Edema of Brain
		Right Side	Left Side		
1	..	3	1	34	Dura distended with fluid
2	..	Elevation	Elevation	134	Considerable excess of cerebrospinal fluid
3	..	1 to 2	1	158	No comment
4	30	4+	4+	54	No comment
5	32	4	4	657	Flattening of convolutions
6	..	2	2	108	Brain swollen
7	..	3	1+	24	No comment
8	..	2 to 3	2 to 3	492	Gyri widened and flattened; sulci narrow; evidence of increased intracranial pressure
9	..	Edema, no definite elevation		144	Convolutions flattened; cortex slightly narrowed, owing to edema of brain
10	..	2	2	285	No comment
11	35	4 to 5	3 to 4	126	Convolutions flattened, grade 1+
12	16	1	1	116	No comment
13	20	1	2 to 3	42	No comment
14	8	Edema, no definite elevation		64	Brain edematous, grade 2+
15	28	7 to 8	7 to 8	86	Marked edema of brain
16	..	Edema, some elevation		101	Atrophy of convolutions, especially frontal, with increased amount of cerebrospinal fluid
17	..	2 to 3	2 to 3	116	Convolutions flattened, grade 1+; sulci narrowed

by Pickering [11] in England. The American authors stated that of 20 patients with severe hypertension in whom they observed an elevation of spinal fluid pressure, 19 had papilledema. Of 30 persons with hypertension in whom spinal fluid pressure was normal, only 2 had papilledema. Of 4 in whom blurring of the margins of the disks was present without definite elevation, all had normal pressures. Pickering reported

10. Shelburne, S. A.; Blaine, D., and O'Hare, J. P.: The Spinal Fluid in Hypertension, J. Clin. Investigation **11**:489-496 (May) 1932.

11. Pickering, G. W.: The Cerebrospinal Fluid Pressure in Arterial Hypertension, Clin. Sc. **1**:397-413 (Dec.) 1934.

that increased pressure in the subarachnoid fluid in patients with hypertension is an exceedingly grave prognostic finding. In the present series of cases the occurrence of increased pressure likewise proved of grave prognostic significance. Patients in whom Pickering observed a pressure of the cerebrospinal fluid exceeding 25 cm. of water all died in from one day to ten months after the lumbar puncture. Of 13 such patients, 10 died of "uremia" and 3 of "convulsions." Both the American and the English workers have found, as I have, that not all patients who present the characteristic retinitis with papilledema and elevated spinal fluid pressure have evidence of renal insufficiency. Merritt and Fremont-Smith [12] stated that, except in rare instances, an elevated pressure of the cerebrospinal fluid occurs in hypertensive patients only if there is uremia, but in the present series of patients there were 2 (cases 4 and 13) who had elevated cerebrospinal pressure without uremia. At the meeting of the Société médicale des hôpitaux de Paris held on Jan. 7, 1938, Riser, Planques and Becq,[13] of Toulouse, reported that 4 patients with hypertension had died after lumbar punctures had been performed. Shelburne, Blaine and O'Hare [10] stated that 1 of their group became psychotic shortly after a lumbar puncture. In the present series of cases, no accident has occurred after this procedure.

ARTERIOSCLEROSIS AND THE BRAIN IN HYPERTENSION

Sclerosis of the Larger Arteries.—In the brain, as elsewhere in the body, sclerosis of the larger arteries appears to present a separate problem from that of the vascular effects of hypertension. The disease that is denoted clinically as arteriosclerosis of the central nervous system is associated pathologically with narrowed irregular tortuous basal arteries, beading and tortuosity of the smaller cortical arteries, thickening and opacity of the arachnoid and atrophy of the cortex with lipoidal degeneration of the neurons. In a group of patients with cerebral arteriosclerosis, Woltman [14] found that 64.4 per cent had a mean blood pressure of 130 systolic and 78 diastolic. Certainly, then, arteriosclerotic changes cannot be considered as due primarily to the effects of hypertension. Indeed, Wartman [15] could find gross arteriosclerotic changes in 80 per cent of brains in an unselected series of autopsies.

12. Merritt, H. H., and Fremont-Smith, F.: The Cerebrospinal Fluid, Philadelphia, W. B. Saunders Company, 1937.

13. Accidents Following Lumbar Puncture in Cases of Hypertension, Foreign Letters (Paris), J. A. M. A. **110**:1056 (March 26) 1938.

14. Woltman, H. W.: Cerebrospinal Arteriosclerosis, Minnesota Med. **5**:102-107 (Feb.) 1922.

15. Wartman, W. B.: The Incidence and Severity of Arteriosclerosis in the Organs from Five Hundred Autopsies, Am. J. M. Sc. **186**:27-35 (July) 1933.

In the 17 patients of the present group the clinical grade of sclerosis of the peripheral arteries (a grading based on palpation of the brachial, radial, temporal and dorsalis pedis arteries) varied from "little" to grade 3 plus on a basis of 1 to 4 (table 2). It would seem from this that there is no constant relation of the severity of arteriosclerosis in the large peripheral arteries to the severity of hypertension. Hypertension was marked in all patients in this group, yet often there was only slight arteriosclerosis; thus, in 1 instance sclerosis was said to be slight, in 1 it was graded only 1 plus and in 4 it was graded 2. In several instances the data permitted comparison of the degree of

TABLE 2.—*Grade of Arteriosclerosis in Cases of Malignant Hypertension*

Case	Grade of Arteriosclerosis *		
	Large Cerebral Arteries	Retinal Arteries	Peripheral Arteries
1	2 to 3	Present	2
2	3	Present	3
3	1	2	2
4	2	2 to 3	1+
5	0	2+	?
6	2	2 to 3	2
7	1	2 to 3	2 to 3
8	1	3	3
9	3	3	3+
10	2	Present	3
11	2	3+	?
12	2	1+ to 2	?
13	3	2+	3
14	1	1 to 2	2
15	0	0	Little
16	3	Considerable	3
17	2+	2+	2+ to 3

* On the basis of 1 to 4.

sclerosis in the peripheral arteries with the degree of sclerosis observed by the ophthalmologist in the retinal arteries and arterioles. In most of these cases the disease was approximately of the same severity in the two sites (table 2). Thus, when a severe grade of sclerosis of the peripheral arteries is present in a patient with this disease, it would appear that the retinal vessels are usually similarly diseased. It is also of interest to compare the severity of the arteriosclerosis in the retinal and peripheral vessels with the degree of arteriosclerosis in the large vessels at the base of the brain. Severe changes in the retinal and peripheral arteries in these patients usually connoted a similar degree of change in the cerebral vessels (table 2). Thus, if one may judge from this small group, the presence of severe arteriosclerosis in the large peripheral and retinal arteries in a patient with malignant hyper-

tension usually indicates that a similar advanced degree of the arterial disease is present in the large cerebral vessels. Occasionally, however, this association is not striking (cases 7 and 8).

The Changes in Cerebral Arterioles.—At various times during the past ten years there have been reports from this institution dealing with extensive surveys of the blood vessels in various organs as affected by hypertension. This series of researches now includes a general survey of the arterioles throughout the body in cases of malignant hypertension;[4] a histologic study of the changes in the arterioles in specimens of pectoral muscle taken for biopsy in cases of hypertension,[6] a clinicopathologic study of the kidney and its vessels in cases of malignant hypertension, which appeared in 1934;[7] a study of the vessels of the spleen, liver, pancreas and gastrointestinal tract,[8] and a study of the heart.[9]

The changes that these workers have described in the arterioles of patients suffering from malignant hypertension are as follows: a slight increase in perivascular connective tissue; hypertrophy of the muscular coat of the media with an increase in the number of nuclear elements; a hyperplastic change affecting the internal elastic lamina, and proliferation of the endothelial and subendothelial cells, which sometimes is so extensive as to occlude the lumen almost completely. One of the outstanding achievements of these studies has been the establishment, by a reasonable biometric method, of data concerning the relative severity of arteriolar changes in persons suffering from hypertension of varying grades of severity. Furthermore, these studies have shown clearly that arterioles of different viscera are involved to differing degrees in the same patient. These workers have all used for measuring the vessels the plan outlined by Kernohan, Anderson and Keith.[5] By this method the thickness of the arteriolar wall is measured in four places, and then an average of these four values is compared with the average diameter of the lumen, established by two measurements made at right angles to each other. The resulting ratio, when studied for a large number of vessels, gives some indication of the increased resistance that the flow of blood must encounter in the organ studied. The method has been adopted elsewhere by various workers,[16] who have confirmed its usefulness.

Histologic studies were made of the 17 brains in this series, with special regard to the changes that had occurred in the measurements

16. (*a*) Pilcher, J. F., and Schwab, E. H.: Arteriolar Changes in Essential Hypertension: A Preliminary Report, Texas State J. Med. **28**:665-668 (Feb.) 1933. (*b*) Murphy, F. D., and Grill, J.: So-Called Malignant Hypertension: A Clinical and Morphologic Study, Arch. Int. Med. **46**:75-104 (July) 1930. (*c*) Moritz, A. R., and Oldt, M. R.: Arteriolar Sclerosis in Hypertensive and Non-Hypertensive Individuals, Am. J. Path. **13**:679-728 (Sept.) 1937.

of the arterioles. Similar studies were also made of brains of 15 persons in whom there had been no evidence of hypertension during life or at autopsy. The disease causing the death of the control patients varied (table 3). Observations of the blood pressure had been made during life in all of the controls. The blood pressures never exceeded 140 mm. of mercury systolic or 90 mm. diastolic, and the weights of the heart at autopsy all fell within the range of normal; that is, they did not exceed 400 Gm. for the men and 350 Gm. for the women. The 15 control patients were chosen in such a manner that the age and sex corresponded to those of the group with hypertension (cases 16 and

TABLE 3.—*Control Series*

Number	Age, Yr.	Sex	Cause of Death	Weight of Heart, Gm.	Mean Ratio of Wall to Lumen, Entire Brain
1	41	♀	Pneumonia	300	1:4.8
2	53	♀	Chronic pulmonary tuberculosis; pneumonia	235	1:3.3
3	47	♂	Cerebral contusions and lacerations	382	1:3.1
4	32	♂	Fractured skull with lacerations of brain	346	1:3.1
5	23	♂	Retrovertebral abscess	287	1:3.7
6	19	♂	Cerebral contusions and lacerations	345	1:3.5
7	57	♂	Carcinoma of ileum; peritonitis	285	1:3.2
8	28	♂	Knife wound of neck	336	1:3.3
9	50	♂	Cancer of larynx with obstruction	327	1:3.0
10	57	♂	Cancer of rectum; pneumonia	212	1:3.3
11	49	♀	Stricture of bile ducts; hepatic coma	312	1:3.4
12	59	♂	Cancer of stomach	242	1:3.6
13	58	♂	Cerebral contusions and lacerations	335	1:3.3
14	30	♀	Chronic ileus with obstruction	230	1:4.4
15	6	♀	Contusions and lacerations of brain	130	1:4.2
			Mean ratio of wall to lumen		1:3.5

17 were added at the end of the work, and no cases were included as controls).

The tissues studied were taken from material obtained at routine necropsy, fixed in 10 per cent solution of formaldehyde U. S. P., blocked in paraffin and stained. The differential stains used to study the vessels included the Van Gieson stain, the Mallory-Heidenhain and the Weigert elastic tissue stain.

As a result of the careful experiments of Moritz and Oldt,[16c] it is now known that methods of preparation of tissues and the physiologic condition of the vessel wall at the time of death have no influence on the ratio of the wall to the lumen as determined by the methods used in my study.

The thickness of the walls and the diameters of the lumens were studied in ten vessels in each of six regions of the brain. These regions were in each instance: the frontal cortex, the parietal cortex, the occi-

pital cortex, the hypothalamic area, the medulla and the meninges. Measurements were made according to the technic of Kernohan, Anderson and Keith.[5] The average for ten vessels from each region was taken to be an indication of the nature of the vessels in that part of the brain. The outside diameter of the vessels studied fell approxi-

TABLE 4.—*Mean Ratio of Wall of Arterioles to Lumen in Different Regions of Body*

Region	Ratio	
	Persons Who Did Not Have Hypertension	Persons Who Died of Malignant Hypertension
Pectoral muscle (Kernohan, Anderson and Keith)..	1:2.0	1:1.1
Kidney (Cain).....	1:1.82	1:0.7
Heart (Odel).....	1:2.00	1:1.95
Abdomen (Morlock)		
Pancreas.....	1:2.45	1:1.24
Liver.....	1:2.31	1:1.14
Gastrointestinal tract.....	1:2.13	1:1.14
Spleen.....	1:1.32	1:1.04
Brain.....	1:3.5 *	1:1.7 †

* The ratio was computed from 900 vessels.
† The ratio was computed from 1,020 vessels.

TABLE 5.—*Mean Ratio of Wall of Cerebral Arterioles to Lumen in Different Regions*

Region	Ratio	
	Persons Who Did Not Have Hypertension*	Persons Who Died of Malignant Hypertension†
Frontal cortex.....	1:3.3	1:1.5
Parietal cortex.....	1:3.3	1:1.5
Occipital cortex.....	1:3.2	1:1.2
Hypothalamic area.....	1:3.8	1:1.8
Medulla.....	1:3.8	1:1.8
Meninges.....	1:3.6	1:1.8

* Each ratio was computed from 150 vessels measured.
† Each ratio was computed from 170 vessels measured.

mately between 20 and 80 microns; thus, my results are comparable to those of the men who have preceded me in this work at this institution (tables 4 and 5 and figs. 2 and 3). For the cerebral arterioles studied, it was found that the mean ratio of wall to lumen was 1 : 1.7 for the brains of persons that had died of malignant hypertension, whereas for the normal controls this mean ratio was 1 : 3.5 (table 4). Different

regions of the brain were noted to have only slightly differing values for these ratios, and these slight variations were noted both in the control group and in the persons who had died of hypertension (table 5).

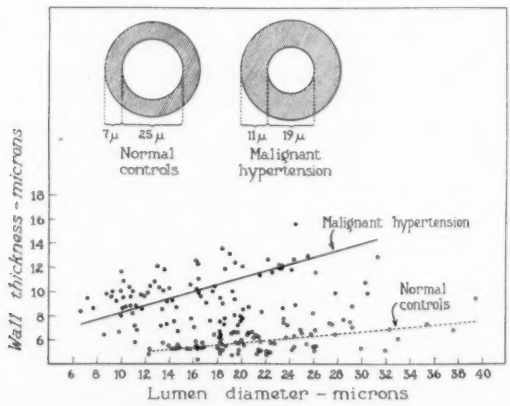


Fig. 2.—Comparison of the thickness of the wall and the diameter of the lumen of cerebral arterioles in cases of malignant hypertension and in the control series. The continuous lines represent the means for these measurements in each group. Arterioles in brains of persons suffering from hypertension have thicker walls than those of the controls, and for a wall of given size the lumen is narrower in the arterioles of persons suffering from hypertension than in those of the controls. Inserts, drawn to scale, illustrate diagrammatically the relative mean measurements for the cerebral arterioles in persons suffering from malignant hypertension and in the controls.

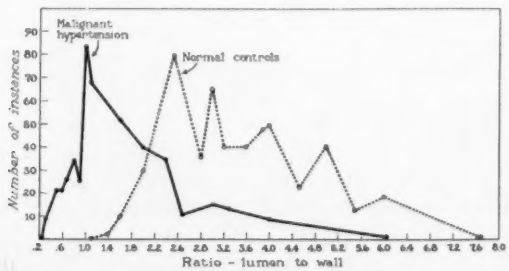


Fig. 3.—Frequency distribution of the ratios of the diameter of the lumen to the thickness of the arteriolar wall for the controls and for persons suffering from malignant hypertension. There is overlapping of the two curves, but the peaks are significantly separated.

Histologic Study of the Arterioles.—A histologic study of the cerebral arterioles must take into account the changes in these vessels that result simply from aging. This subject recently was reviewed by

Baker,[17] who concluded that the cerebral arterioles are distinguished from those elsewhere in the body by several features: (1) The internal elastic lamina of the cerebral vessels is thicker than in vessels of similar size elsewhere; (2) collagen (hyalin) may make up the bulk of the wall of the cerebral arterioles, the muscle being irregular in occurrence or often entirely absent; (3) as the vessel diminishes in size its structure becomes simpler, so that what would be called fibrosis elsewhere is normal for the cerebral arteries. Baker found that with age (and independent of hypertension) there occur: (1) thickening and reduplication with fraying of the internal elastic lamina and (2) progressive reduction in the muscular elements of the media with replacement by fibrous tissue. General thickening of the arteriolar wall with reduction of the caliber of the lumen was not noted by Baker as a feature of the changes in these vessels due to age.

On the other hand, thickening of the wall of arterioles was encountered in many sections that I examined from the brains of patients with hypertension, and this thickening was usually associated with reduction of the caliber of the lumen. In a general way, this thickening was due to an increase in the thickness of each of the three coats of the vessel (fig. 4). Thus, in intimal lining, the muscular media and the fibrous adventitia took part in the changes observed. There was considerable variation in the extent to which these coats participated in the thickening. Intimal proliferation was seen frequently, but by no means in all the vessels encountered (fig. 5). As a cause of general reduction of the width of the arteriolar stream bed of the brain, intimal proliferation appeared less important than the changes that occurred in the medial coat. Little degeneration was seen in the intimal or the medial coat. Vacuolar and hydropic degeneration was insignificant as a pathologic feature of these vessels, as were hyalinization and necrosis. The latter degenerative changes appeared to occur only as end stages in the disease process that affected the arterioles in malignant hypertension (fig. 6).

The internal elastic lamina partook of the general hypertrophy affecting the vessel wall, and when examined in the specimens stained with an elastic tissue stain, this layer was usually seen to be comparatively thicker than in similarly sized vessels in control specimens. Not uncommonly this thick lamina was frayed or reduplicated, and with the elastic tissue stain strands of fibers could be seen to ramify throughout the other coats of the vessel (figs. 5 and 7). This is the so-called elastosis. This ramification of elastic fibers also occurs occasionally in normal vessels, but the fibers are much less thick than in vessels from

17. Baker, A. B.: Structure of the Small Cerebral Arteries and Their Changes with Age, Am. J. Path. **13**:453-461 (May) 1937.

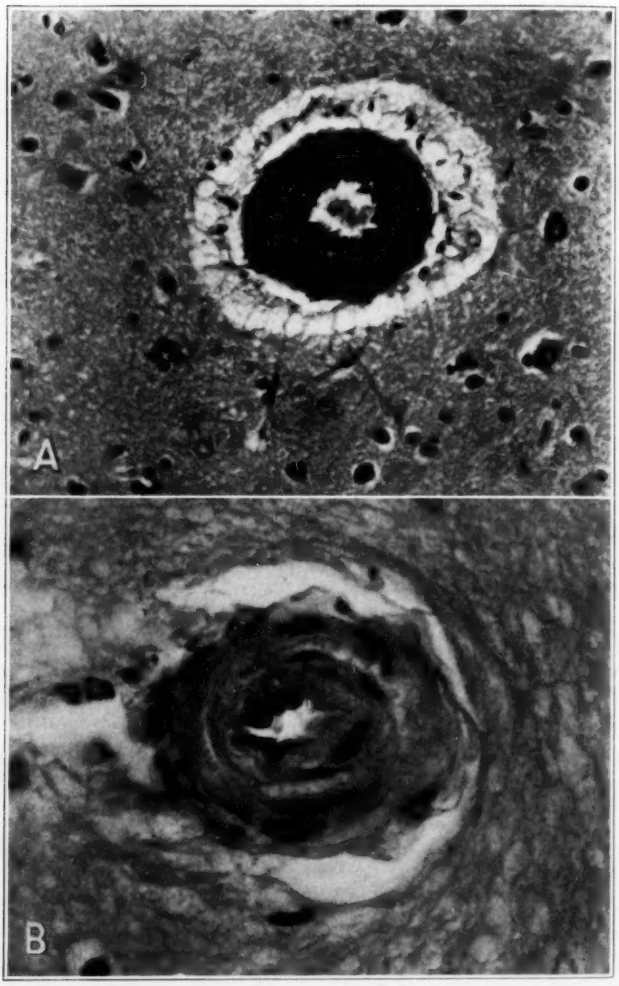


Fig. 4.—*A* (case 17), section from the occipital lobe (× 300), showing markedly hypertrophied arteriolar wall with narrowed caliber of the lumen. *B* (case 13), section from the left frontal lobe (× 480), showing markedly hypertrophied arteriolar wall with narrowed caliber of the lumen. Slight hyaline changes are evident in the wall. Hematoxylin and eosin.

the brains of patients with hypertension and consequently much more difficult to follow in the microscopic preparations. Fractures in the internal elastic lamina are not uncommon in the vessels of persons suffering from malignant hypertension.

In the medial coat of many arterioles in the brains of persons with hypertension, there could be seen an increase in the size of the individual cells and of their nuclei, and often there appeared to be

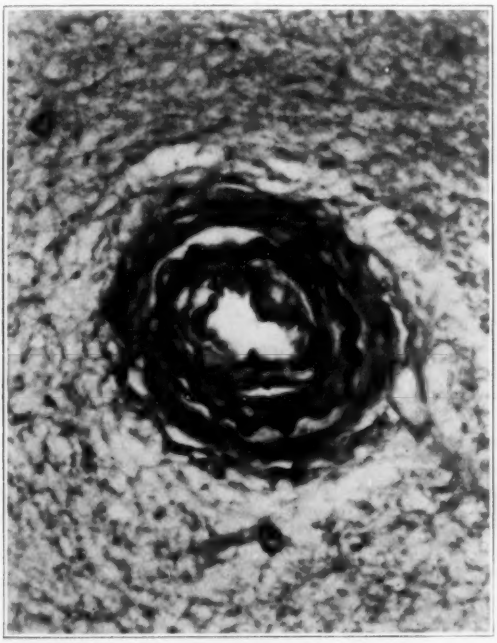


Fig. 5 (case 12).—Arteriole in the region of the right parietal lobe, showing hypertrophy of arteriolar wall, thickened frayed internal elastic lamina and hyperplasia with thickening of the intimal coat. Weigert elastic tissue stain; × 700.

such an increase in the number of cells that this portion of the wall was thick and hypertrophic. The adventitial fibrous coat was frequently thickened, and in the Van Gieson-stained sections it often appeared as a red band about the vessel. I have seen little infiltration of the medial or the intimal coat with fibrous tissue cells, although the adventitial fibrous coat was in general thick as compared with that of normal vessels. Not uncommonly one found a few lymphocytes in the thickened adventitial coat, and in a number of brains examined these peri-

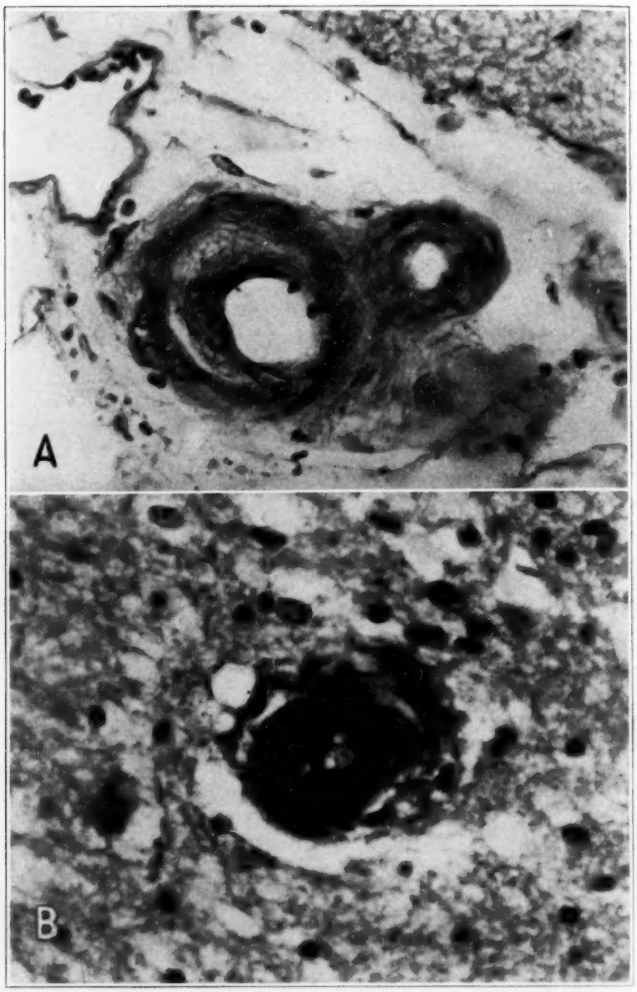


Fig. 6.—*A* (case 3), arterioles in the meninges, showing hypertrophy of the walls with vacuolar degeneration; × 400. *B* (case 15), arteriole in the region of the parietal lobe, showing hypertrophy and marked necrosis, with hyaline degeneration of the wall; × 780. Hematoxylin and eosin.

vascular lymphocytes had increased in number to form a definite collar about the vessels, as described in the section on "inflammatory lesions." Calcification was rare in the cerebral arterioles, being seen only occasionally as a band of calcified droplets lying between the medial and the adventitial coat.

Accordingly, the study of the arterioles in the brain reveals that there is often present hypertrophy of arteriolar walls with reduction of the caliber of the lumen. It would appear that a definitely increased

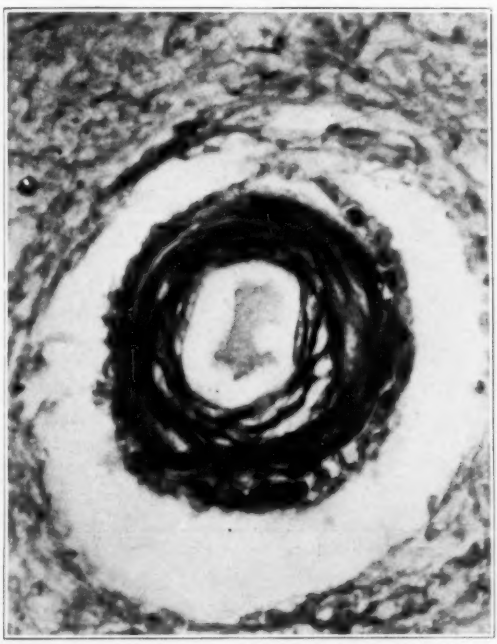


Fig. 7 (case 3).—Arteriole in the region of the left frontal lobe, showing hypertrophy and fraying of the arteriolar wall, with lamination and thickening of the internal elastic lamina. Weigert elastic tissue stain; × 700.

anatomic barrier often exists in this disease, which may obstruct the flow of blood beyond the degree of resistance normally offered by this arteriolar portion of the vascular tree. For some unknown reason, not every tissue shares alike in the extent of change in the disease, but the brain is frequently severely affected. The heart usually escapes with slight changes.[9] Essentially, the lesions in the brain observed in the patients who had suffered from malignant hypertension were similar to the changes that other investigators have found in persons with

benign hypertension. They differed only in their advanced degree and severe nature. Necrosis of arterioles, which has not infrequently been described as the sine qua non of malignant hypertension, was extremely rare in these specimens. In table 6 I have correlated the severity of the changes in the caliber of the cerebral arterioles with the occurrence of destructive cerebral lesions. It appears that no definite relationship exists between these data.

In 1926 Bordley and Baker [18] published a study of the brain in cases of hypertension. They concluded that arteriosclerosis is more marked in the medulla than elsewhere in the brain in such cases and that it is possible to explain chronic hypertension on the basis of localized

TABLE 6.—*Cerebral Vascular Lesions and Ratio of Wall of Cerebral Arterioles to Lumen in Cases of Malignant Hypertension* *

Case	Massive Hemorrhage	Large Infarct	Multiple Small Hemorrhages	Multiple Small Infarcts	Average Ratio of Wall to Lumen
1	+	..	+	+	1:1.8
2	..	..	+	+	1:2.02
3	..	..	+	+	1:1.5
4	+	+	+	+	1:1.6
5	..	..	+	..	1:2.8
6	+	..	..	..	1:1.3
7	+	..	+	+	1:2.1
8	..	..	+	+	1:2.5
9	..	..	+	+	1:1.9
10	..	..	..	..	1:1.3
11	..	..	+	..	1:1.4
12	..	..	..	+	1:1.2
13	..	..	+	+	1:1.4
14	..	..	+	..	1:1.2
15	..	+	..	+	1:1.3
16	..	..	+	+	1:2.0
17	..	+	+	+	1:1.6

* The presence of the lesion is indicated by +.

arteriosclerosis in the region of the vasomotor center. This arteriosclerosis, they concluded, probably results in local anemia, which, according to the experiments of Anrep and Starling,[19] would give rise to systemic hypertension. This conception has been vigorously and adequately opposed by many workers (Rühl, 1927;[20] Keith, Wagener and

18. Bordley, J., III, and Baker, B. M., Jr.: A Consideration of Arteriosclerosis of the Cerebral Vessels and the Pathogenesis of Hypertension: A Preliminary Report, Bull. Johns Hopkins Hosp. **38**:320-321 (April) 1926; Arteriosclerosis of the Cerebral Vessels and the Pathogenesis of Hypertension, ibid. **39**:229-264 (Oct.) 1926.

19. Anrep, G. V., and Starling, E. H.: Central and Reflex Regulation of the Circulation, Proc. Roy. Soc., London, s.B **97**:463-487 (Feb. 2) 1925.

20. Rühl, A.: Wie weit ist der genuine arterille Hochdruck anatomisch bedingt? Deutsches Arch. f. klin. Med. **156**:129-161 (Aug.) 1927.

Kernohan,[4] 1928; Cutler,[21] 1928, and Tuthill, 1931 [22]). My measurements of the arterioles of the medulla in 17 patients with severe hypertension show considerable narrowing of the lumen. However, this does not appear to be more marked than for any other of the regions studied (table 5).

CEREBRAL LESIONS IN MALIGNANT HYPERTENSION

The brain is seriously damaged in malignant hypertension. Probably no vital organ save the kidney is more uniformly or more extensively involved by this disease. A review of the lesions that were observed in the brains in the present series will serve to illustrate this fact.

The two major pathologic processes that damage the brain in malignant hypertension are hemorrhage and infarction.

Hemorrhage.—A large variety of sites and a considerable variation in form characterized the hemorrhages in these brains. Among the 17 brains studied, there were 4 with massive hemorrhage. The brain in case 6 is typical. A large cavity filled with blood, involving the corpus striatum and the internal capsule, was observed in the left hemisphere. The hemorrhage had ruptured into the ventricles. This was a death-dealing blow for the patient, who died within twelve hours after symptoms of it appeared. In each of these 4 instances the large hemorrhage had torn its way into the ventricles. In 3 of these the hemorrhage was cerebral and had ruptured into the lateral ventricles, and in 1 it was cerebellar and had ruptured into the fourth ventricle. Death always occurred promptly when the hemorrhage ruptured into the ventricular system. Severe renal insufficiency was present in 1 instance (case 6) and absent in 3 (cases 1, 4 and 7) when the large hemorrhage occurred.

A second variety of hemorrhage encountered was small and spotty, consisting of regions of hemorrhage measuring from 1 mm. to 2 cm. in diameter (fig. 8). These were distributed irregularly throughout the white matter of the cerebrum and cerebellum in 5 instances (cases 2, 3, 8, 16 and 17). Microscopic examination showed some to be homogeneous regions of hemorrhage without obvious source and others to be so-called ring hemorrhages, or circular zones of hemorrhage about the small vessels. These small hemorrhages were associated in each case with numerous infarcts of about the same size and distribution as the hemorrhages. In all these 5 cases there was marked nitrogen retention at the time of death, the last recorded values for blood urea being 134, 158, 492, 101 and 116 mg. per hundred cubic centimeters, respectively.

21. Cutler, O. I.: Relation of Arteriosclerosis of the Cerebral Vessels to Hypertension: Distribution of Arteries Supplying Pons and Medulla, Arch. Path. **5**:365-379 (March) 1928.

22. Tuthill, C. R.: Hypertension in Relation to the Blood Vessels of the Medulla Oblongata, Arch. Path. **11**:760-765 (May) 1931.

In case 8 the number of hemorrhages was so great that it suggested to Dr. Kernohan hemorrhagic encephalitis of the arsenical type, and chemical analysis showed the presence of 0.12 mg. of arsenic per hundred grams of brain substance. In certain types of encephalitis, the presence of arsenic in excess of 0.1 mg. per hundred grams is believed to be of etiologic significance. However, the relationship of the arsenic to the hypertension in this instance is not clear.

Fig. 8 (case 8).—Small, "spotty" hemorrhage and "ring hemorrhage" in a section from the thalamus. Hematoxylin and eosin; × 60.

Bleeding onto the surfaces of the brain occurred in cases 1, 14 and 17. In case 1 small hemorrhages were found beneath the arachnoid, scattered about the surface of the cerebral and cerebellar hemispheres and penetrating between the convolutions. In case 14 the hemorrhages were subdural. In case 17 there was a small region of subarachnoid hemorrhage over the superior surface of the right parietal lobe. Subependymal hemorrhage was found in the anterior horn of the lateral ventricle in case 7.

Capillary hemorrhages were observed frequently (fig. 9). They were ever more common than any of the three types of bleeding just

described and occurred in 8 instances (cases 2, 3, 4, 5, 9, 11, 13 and 14). Of these instances, severe renal insufficiency was present in 6 (cases 2, 3, 5, 9, 11 and 14) and absent in 2 (cases 4 and 13).

Of these various forms of hemorrhage, the massive and the spotty were definitely destructive of brain tissue and doubtless were responsible for symptoms during the life of the patient. The capillary hemorrhages may also have caused considerable irritation to the brain. Furthermore, the frequent association of the different types of hemorrhage with one

Fig. 9 (case 2).—Minute capillary hemorrhages in a section from the region of the hypothalamus. Hematoxylin and eosin; × 55.

another and with other types of lesions in the same brain probably means that in these instances considerable portions of the brain had been thrown out of function.

Infarctions.—Infarcts in these brains are divided into two varieties: single large and multiple miliary infarcts.

Single large infarcts were observed in cases 4, 15 and 17. In case 4 the infarct doubtless dated from a cerebrovascular episode which, according to the history, had occurred six months before death. This infarct involved the basal ganglions on the left, measured 0.5 by 4 by 6

cm. and was associated with a large recent hemorrhage on the right side which had ruptured into the ventricles. In the second instance (case 15) the large single infarction took place in a child aged 7 years and appeared grossly as widespread necrosis of the surface of the left side of the brain, involving the temporal, occipital and parietal lobes. Roughly, this necrotic region corresponded to the surface distribution of the middle cerebral artery. On section of the brain the infarct was shallow, involving only the gray matter and the adjoining white matter. Doubtless this infarct was superficial rather than deep because of some peculiarity of the collateral circulation in the brain of the child. In case 17, the infarct was similar to that observed in case 4. In these 3 cases there were small multiple infarcts in addition to the large infarct.

Multiple miliary infarcts, the second form, must be of outstanding importance in these cases because of the frequency with which it occurs and its wide distribution. These multiple miliary infarcts were found in 12 instances (table 7 and figs. 10, 11 and 12). They were widespread, involving not only the basal ganglions but also the cortex, the white matter, the basal nuclei, the brain stem and the cerebellum. They varied in size from regions 5 or 6 mm. in diameter to minute softenings seen only with the aid of the microscope. In 4 of these 12 cases no lesion could be seen on gross examination, but the softenings were found in microscopic sections. Thus, the brain cannot be assumed to be intact unless careful microscopic search for these lesions has been made. In the remaining 8 cases both gross and microscopic lesions were observed. It is important to realize that the extent of these infarcts and the amount of cerebral damage that they cause cannot be accurately estimated unless many sections are studied. I was often impressed with the fact that large quantities of brain substance had been destroyed by these infarcts, and the clinical pictures often suggested the same conclusion. Degenerated blood in the form of blood pigment was seen frequently in these infarcts and suggested that the insults had been occurring over long periods, probably in "crops," as Pal [23] suggested. Table 6 illustrates the frequency with which destructive lesions were encountered.

Spielmeyer [24] expressed the opinion that some of these infarcts are due to vasospasms. His opinion was based on the observation of circumscribed regions, necrotic and destroyed, without his being able to demonstrate any obstruction in the vessels. This has often been my own experience. However, some infarcts in this series of brains had

23. Pal, J.: Ueber die zerebralen Insulte und den Angiospasmus der Hypertoniker, Wien. klin. Wchnschr. **44**:1297-1299 (Oct. 16) 1931.

24. Spielmeyer, W.: Vasomotorisch trophische Veränderungen bei zerebraler Arteriosklerose, Monatschr. f. Psychiat. u. Neurol. **68**:605-620 (March) 1928.

adjoining thrombosed vessels (fig. 16). Volhard and Fahr [1] cited this opinion of Spielmeyer as confirming their own hypothesis of the occurrence of "vasospastic insults" in the brain. Hiller [25] cited two good rules for the acceptance of a lesion of the brain as angiospastic: (1) There must be absence of true vascular obstruction in the presence of a lesion, or (2) there must have been absence of a lesion in the presence of loss of function. He expressed the opinion that a pathologist may be able to say whether a lesion has been caused by a vascular disorder and may be able to describe the adjoining vessels but will not be able to state the type of functional vascular change that occurred during life. The last word, he pointed out, will have to wait on studies of the cerebral circulation in the living subject.

At this point are included for comparison figures cited in 1937 by Jaffé [26] regarding the destructive lesions in the brains of patients with essential hypertension. He stated that in 20 per cent of patients with this disease death was directly due to encephalic injuries. Of these 20 per cent, he found infarctions in the brains of 13 per cent and hemorrhage in the remaining 7 per cent. It is of interest to compare these figures with the results of the study of the present group of patients with malignant hypertension. Cerebral hemorrhage caused the death of 4 patients (24 per cent), and some type of destructive lesion was found in 12 (71 per cent) of the entire group of patients with malignant hypertension. Thus the brain suffers destructive lesions with relatively great frequency in this more severe form of the disease.

Inflammatory Lesions.—There is considerable theoretic interest in the presence of inflammatory lesions in tissue from patients with severe hypertension. The cause of this disease has at various times been attributed to bacteria, and a case of severe vasospastic hypertension was recently reported from the Mayo Clinic in which the patient recovered after removal of infected tonsils.[27] Klemperer and Otani [28] and, recently, Rosenberg, Keith and Wagener [29] have reported instances of severe hypertension in which marked inflammatory reactions could be seen in many blood vessels.

---

25. Hiller, F., in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol. 11, pp. 331-338.

26. Jaffé, R. H.: The Pathology of the Cardiovascular, Cerebral and Renal Changes in Essential Hypertension, Radiol. Rev. & Mississippi Valley M. J. **39**: 7-12 (Jan.) 1937.

27. Habein, H. C., and Wagener, H. P.: Acute Vasospastic Hypertension, Minnesota Med. **20**:180-182 (March) 1937.

28. Klemperer, P., and Otani, S.: Malignant Nephrosclerosis (Fahr), Arch. Path. **11**:60-117 (Jan.) 1931.

29. Rosenberg, E. F.; Keith, N. M., and Wagener, H. P.: Diffuse Arterial Disease with Hypertension: Two Unusual Cases of Contrasting Types, Arch. Int. Med. **62**:461-481 (Sept.) 1938.

TABLE 7.—*Data on Persons Who Died of Malignant Hypertension*

Case, Sex and Age	Terminal Urea, Mg. per 100 Cc. of Blood	Cerebral Symptoms	Neuropathologic Observations	Postmortem Observations in Brain				Comment
				Edema	Hemorrhages	Infarcts	Inflammatory Features	
1 ♀ 45	34	Transient hemiplegia; tinnitus; impaired memory; vertex headaches; terminal hemiplegia with aphasia	None until onset of hemiplegia	Dura distended with fluid	Large hemorrhage of right cerebral hemisphere with rupture into ventricles; multiple small subarachnoid hemorrhages	Numerous microscopic infarcts	None	Multiple miliary infarctions of brain with clinical history of cerebral episodes, including transient hemiplegia
2 ♀ 55	134	Emotional; periods of confusion; attacks of numbness of right arm; terminal coma	None	Considerable excess of cerebrospinal fluid	Hemorrhage 2 cm. in diameter in left cerebral hemisphere; multiple capillary hemorrhages	Numerous miliary infarcts	Foci of gliosis; perivascular cuffings	Numbness of right arm referable to hemorrhage of left cerebral hemisphere; marked cerebral symptoms during life, with much destruction of brain; negative objective results of neurologic examination
3 ♂ 50	158	Convulsions followed by deep coma 2 mo. before death; intense restlessness, confusion, delirium	None before convulsion, then left Babinski sign	No comment	Numerous small, spotty hemorrhages; widspread capillary hemorrhages	Numerous miliary infarcts	Perivascular cuffings; foci of astrocytes	Convulsions and abnormal mental state during life; hemorrhages and infarcts in cerebrum; objective results of neurologic examination negative despite much cerebral damage
4 ♂ 22	54	Paralysis right side (4 mo. before death); then restlessness, convulsions, bright red blood in cerebrospinal fluid	Residual right hemiplegia	No comment	Large hemorrhage in right internal capsule, rupture into ventricles; multiple capillary hemorrhages	Old large infarct in cerebrum; numerous miliary infarcts	.....	Extensive cerebral destruction
5 ♂ 27	657	Severe occipital headaches 10 wk., drowsiness 1 mo. before death	None	Flattening of convolutions due to edema	Capillary hemorrhages	.....	Foci of glial cells in cortex; perivascular cuffings	Severe headaches before death; edema of brain at autopsy
6 ♂ 22	108	Severe headaches 1 wk.; terminal staggering, coma	.....	Swelling of brain	Large hemorrhage of left hemisphere with rupture into ventricles	.....	.....	Negligible cerebral symptoms until final episode of large hemorrhage, causing death
7 ♂ 52	24	Transient coma; attacks of severe headache; convulsions over 23 mo.; terminal sudden coma with convulsions	Persistently negative	No comment	Large hemorrhage in cerebellum, rupture into ventricles; subependymal hemorrhages of lateral ventricle	Multiple miliary	Perivascular cuffing	Recurring transient cerebral attacks ending by large cerebral hemorrhage; multiple small infarcts also found in cerebrum

8 ♂ 29	492	Severe headaches 8 mo., with nausea and vomiting; episodic confusion	Negative	Widened gyri, narrowed sulci due to increased pressure	Petechial throughout brain	Multiple miliary	.....	Severe headaches with episodic confusions and edema of brain, with multiple hemorrhages
9 ♂ 54	144	Drowsiness 9 mo.; olfactory and visual hallucinations; episodic confusion; disturbing dreams	Negative	Flattened convolutions due to edema	Capillary in arachnoid	Multiple miliary	Perivascular cuffing; intense gliosis in cerebrum	Severe recurring cerebral attacks during life, with widespread cerebral destruction at autopsy
10 ♂ 55	285	Failing memory, sudden stupor and death	.....	No comment	None	None	Perivascular cuffings	Little clinical cerebral disturbance; no destructive cerebral lesions at autopsy
11 ♀ 47	126	No definite symptoms	Negative	.....	Postoperative streptococcic meningitis; many capillary hemorrhages	.....	Perivascular cuffings	
12 ♂ 57	116	Episodes of staggering and vertigo; severe headaches with nausea and vomiting; attacks of confusion	Bilateral Babinski sign	No comment	.....	Multiple miliary	.....	Severe episodic cerebral symptoms with many miliary infarcts at autopsy
13 ♂ 56	42	Occipital headaches 1 yr.; recurring convulsions	Negative	No comment	Capillary	Multiple miliary	Perivascular cuffings	Recurring convulsions during life; multiple small cerebral infarcts at autopsy
14 ♀ 41	192	Violent headaches; clouded, stuporous mental state 1 mo. before death	Negative	Grade 2+	Capillary; multiple small subdural hemorrhages	.....	Collections of astrocytes in cerebrum	Severe headaches and stupor during terminal illness, with edema of brain at autopsy
15 ♀ 7	86	Severe headaches, recurring convulsions, transient hemiplegia	Negative except homonomous hemianopia	Marked	None	Multiple miliary; single large infarct in left cerebral hemisphere	.....	Episodic cerebral attacks with marked cerebral destruction
16 ♂ 65	101	Failing memory; severe headaches; periodic delirium; intense restlessness	Negative	Increased amount of cerebrospinal fluid	Multiple, spotty	Multiple miliary	Perivascular cuffings	Episodic cerebral attacks with marked cerebral destruction
17 ♂ 47	116	Weakness of left leg; attacks of headaches with vertigo, nausea and vomiting; personality change; terminal convulsion and coma	.....	Flattened convolution and narrowed sulci	Multiple, spotty, subarachnoid hemorrhage in right parietal area	Multiple; small foci; large infarct of right cerebral hemisphere	Foci of marked gliosis; perivascular cuffing	Many varied cerebral symptoms with extensive cerebral destruction

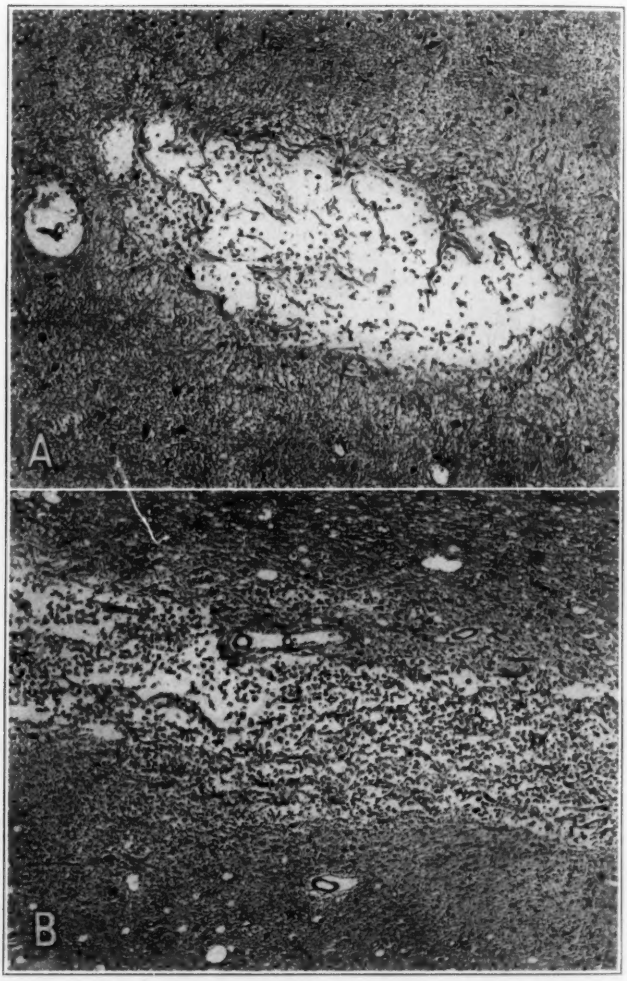


Fig. 10 (case 9).—*A*, minute infarct in a section from the thalamus, showing cystic degeneration. *B*, minute infarct in a section from the thalamus, showing a great number of scavenger cells. Hematoxylin and eosin; × 50.

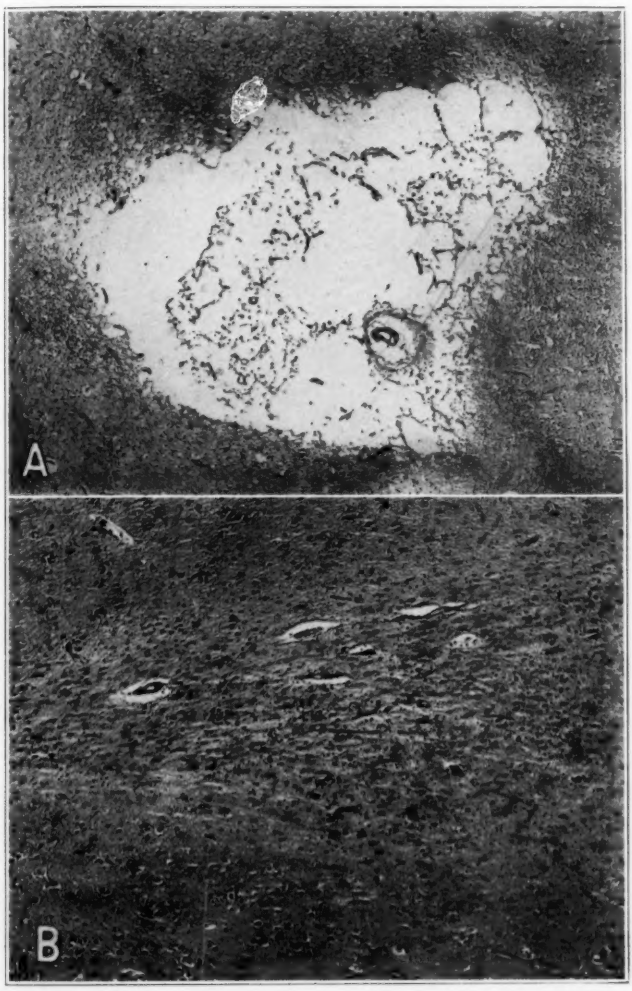


Fig. 11.—*A* (case 3), minute cystic cavity resulting from a small region of infarction in a section from the temporal lobe; × 25. *B* (case 9), glial scar resulting from the healing of a small region of infarction in a section from the thalamus; × 58. Hematoxylin and eosin.

In these 17 brains, collections of lymphocytes were observed about arterioles in 10 (cases 2, 3, 5, 7, 9, 10, 11, 13, 16 and 17). These perivascular collections tended to form distinct cuffs. None of the 10 patients had serologic or other evidence of syphilis. One patient (case 4) with syphilis did not show cuffing of the cerebral vessels. For the most part these cuffings were moderate in degree (figs. 13 and 14). The cuffings were not confined to the immediate neighborhood of infarction or hemorrhage. On the contrary, they were found in regions

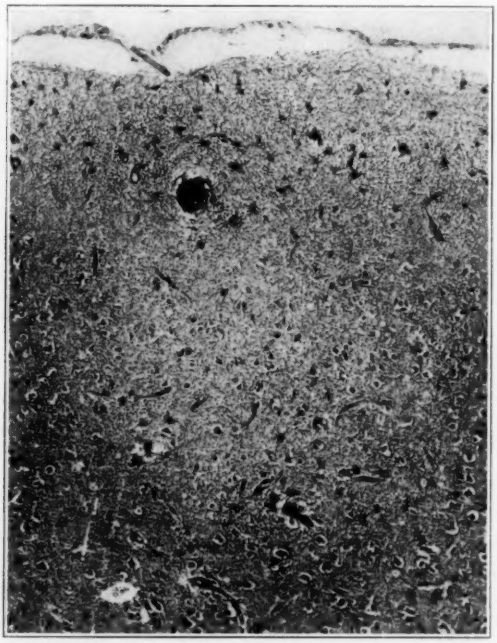


Fig. 12 (case 12).—Section from the left frontal lobe, showing a zone of infarction with loss of neurons, a so-called region of devastation. Note the occluded vessel. Hematoxylin and eosin; × 85.

remote from other lesions. In table 8 the occurrence of cuffing of arterioles is correlated with the presence or absence of uremia and with the nature of the other destructive lesions encountered.

Recent studies by Ecker [30] have shown that in some instances of encephalitis, in which periarteriolar collections of lymphocytes are

30. Ecker, A.: Arsenic and the Nervous System with Special Reference to Subacute and Chronic Encephalitis, Thesis, Minnesota University Graduate School, 1938.

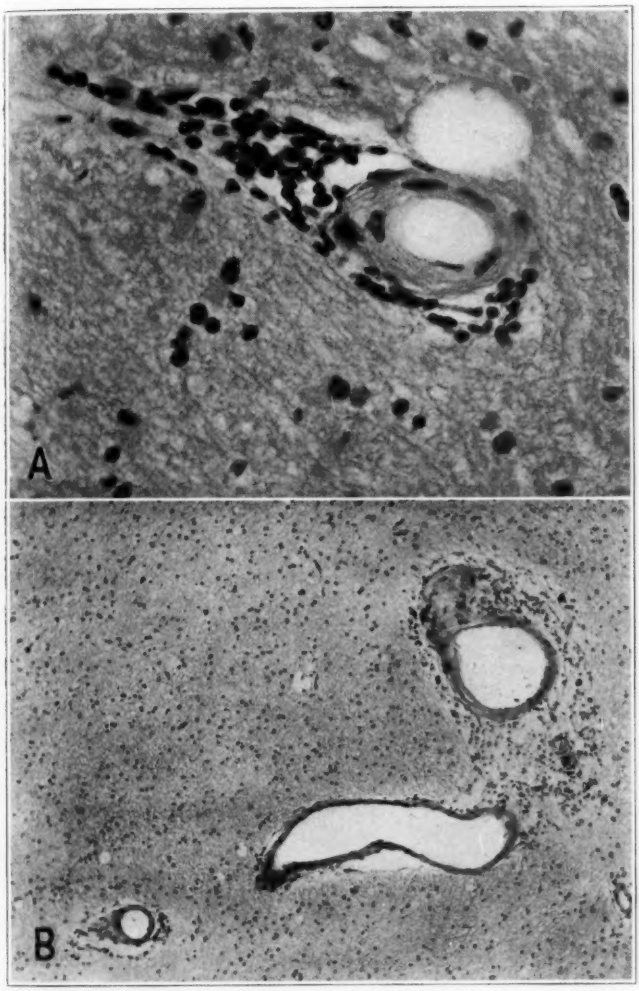


Fig. 13 (case 9).—*A*, hypertrophy of the wall of a small arteriole with periarteriolar collection of lymphocytes in a section from the right occipital lobe; × 460. *B*, perivascular collections of lymphocytes in a section from the thalamus; × 65. Hematoxylin and eosin.

found in the brain, the condition is due to arsenic. Of the 10 brains in the present series in which perivascular cuffing was present, he has analyzed 6 for the presence of arsenic (cases 2, 3, 5, 9, 11 and 13). Using the Osterberg [31] modification of Gutzeit's test, he was unable to find arsenic in any of the 6 brains.

Case 11 ought not to be considered with the other 9 cases because of the probable relation of the cuffing to terminal meningitis, which followed operation. This, however, leaves 9 cases in which this inflam-

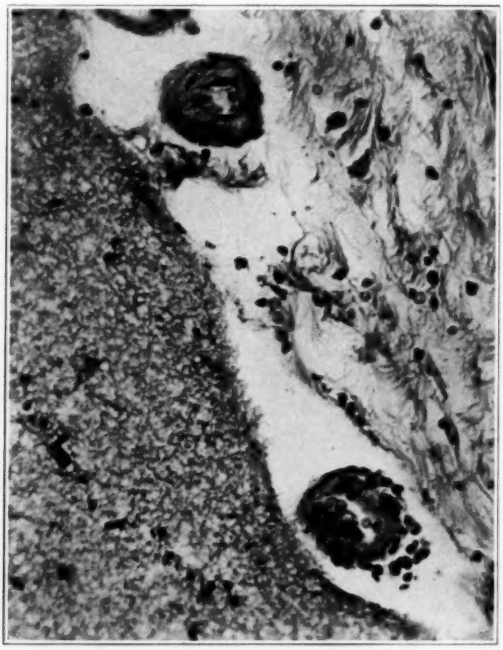


Fig. 14 (case 13).—Meningeal arterioles, showing hypertrophied walls and periarteriolar collections of lymphocytes in a section from the frontal lobe. Hematoxylin and eosin; × 265.

matory response was present without any apparent explanation. The occurrence of this lesion seemed not always to be an expression of a rapid course. It occurred in 1 instance (case 13) in which eighteen months elapsed between the onset of the symptoms and death, and it

31. Osterberg, A. E.: A Modification of the Electrolytic Gutzeit Apparatus for the Estimation of Arsenic in Biological Material, J. Biol. Chem. **76**:19-22 (Jan.) 1928.

also occurred when only four months had intervened (case 3). Severe renal insufficiency was absent in 2 instances (cases 7 and 13), which indicates that this condition alone is not causative. Destructive cerebral lesions were likewise absent occasionally.

These cuffings were different in appearance from perivascular cuffings occasionally seen adjoining regions of large hemorrhage or infarction. In the latter type the cells are predominantly polymorphonuclears which are emigrating from the blood vessels into the perivascular spaces and thence into the necrotic regions, whereas the perivascular cuffings which are observed in the brains of patients dying of malignant hypertension are mainly formed by lymphocytes. The polymorphonuclear cuffings adjoining infarcts or hemorrhages are prob-

TABLE 8.—*Clinical and Postmortem Observations in Cases of Malignant Hypertension in Which Cuffing of Cerebral Arterioles Occurred*

Case	Concentration of Urea, Mg. per 100 Cc. of Blood	Duration of Life, Months After Onset of Symptoms	Destructive Lesions in Brain
2*	134	12	Multiple hemorrhages and infarcts
3*	158	4	Multiple hemorrhages and infarcts
5*	657	13	None
7	24	17	Large hemorrhage of cerebellum
9*	144	9	Multiple hemorrhages and infarcts
10	285	12	None
11*†	126	6	Meningitis, postoperative
13*	42	18	Capillary hemorrhages; multiple infarcts
16	101	6	Multiple hemorrhages and infarcts
17	116	8	Multiple hemorrhages and infarcts

* Analysis for arsenic gave negative results.

† Cuffing probably evidence of encephalitis accompanying meningitis.

ably due to necrosis of tissue and correspond to the polymorphonuclear response to infarcts observed in other organs, such as the heart, kidney and lung. The periarteriolar lymphocytes in these brains affected by hypertension should probably be looked on as an inflammatory, but not necessarily an infectious, response. They may be the result of noninfectious tissue damage.

A second type of inflammatory or proliferative reaction seen in these brains was the proliferation of glial cells (fig. 15). This was observed in 6 brains (cases 2, 3, 5, 9, 14 and 17). In 3 brains (cases 2, 9 and 17) dense accumulations of glial cells of all types, but mainly astrocytes, were seen in the white matter, where ordinarily but few astrocytes are seen. Small focal collections of glial cells were noted about some small vessels in 5 brains (cases 3, 5, 9, 14 and 17). No lesions resembling those of periarteritis nodosa were found in any of the brains. It is

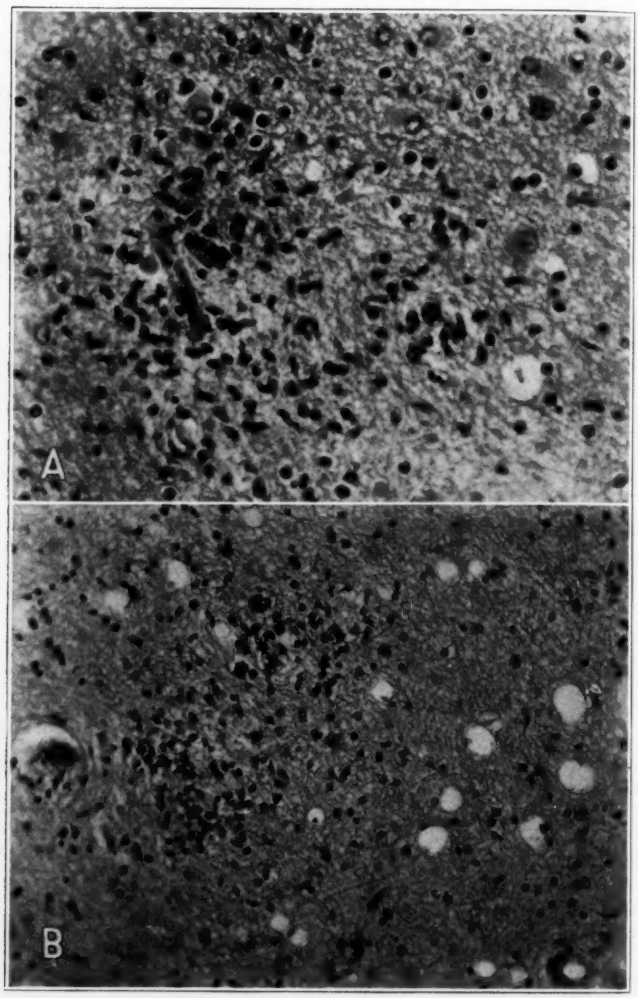


Fig. 15.—*A* (case 17), focal proliferation of glial cells in the white matter of a section from the left parietal region. Many astrocytes (gemästete glia) appear swollen; × 265. *B* (case 9), focal proliferations of glial cells in a section from the thalamus; × 165. Hematoxylin and eosin.

of interest that perivascular cuffings occurred in all but 1 (case 14) of the 6 brains in which glial proliferations were encountered (table 7).

Intracerebral and Extracerebral Edema.—It is important to have information regarding edema of the brain in patients with hypertension because of the possibility of relieving symptoms of this condition during life by means of hypertonic solutions. In table 1 the available data concerning disturbances of intracranial fluids are correlated with (1) the degree of choking of the optic disks, (2) the presence or absence of uremia at the time of death and (3) the pressure of the subarachnoid fluid during life.

Brains that have been preserved in fixative solutions are not satisfactory for studying the presence or absence of edema. Consequently, my data regarding this phenomenon have been taken from the gross and microscopic descriptions of these brains as recorded at the time of the original autopsy. Edema or marked increase in the amount of cerebrospinal fluid was noted by the pathologist in 11 of the 17 cases in this series.

As one might expect, it would appear that the patients with high grades of papilledema often had an increase in the pressure of the cerebrospinal fluid and also showed edema of the brain at autopsy. No instance of "pressure cone" (such as was described by Blackfan [32] in his famous case) was observed in this series.

On microscopic examination it was possible to find some apparent increase in the size of the perivascular and pericellular spaces of these brains, and in places the fiber tracts were widely separated, seemingly by edema fluid, in the form of a meshwork. It is not certain, however, whether these changes resulted from actual increase in the amount of fluid in the brains or from postmortem shrinkage during fixation.

One may conclude from the data in table 1 that intracerebral edema or an increased quantity of cerebrospinal fluid does occur often in malignant hypertension, and that either of these conditions may play a significant role in bringing about an increase in intracranial tension, thus producing symptoms. Signs of these disturbances should be watched for carefully during life, and if such signs appear measures should be instituted to combat them.

Anemia of the Brain.—This condition has been discussed widely as playing a part in causation of the cerebral symptoms that so often accompany severe hypertension. It seems significant that in the autopsy records of the 17 patients no statement can be found that would indicate that an anemic condition of the brain was observed. There was no

32. Blackfan, K. D.: Acute Nephritis in Children, with Special Reference to the Treatment of Uremia, Bull. Johns Hopkins Hosp. **39**:69-90 (Aug.) 1926.

microscopic feature that could be interpreted as being due to general anemia, and there were only such evidences of local anemia as the infarcts.[33]

33. Dr. H. P. Wagener stated: "The average ratio of wall to lumen in normal retinal arterioles which measure 66 to 116 microns in diameter ophthalmoscopically is variously stated as from 1:4 to 1:7. Thus the retinal arterioles present a closer similarity in thickness of wall to the cerebral arterioles than to the arterioles of the peripheral muscles.

With reference to the collections of lymphocytes around the arterioles: Periarteriolar sheathing of the retinal arterioles is found in a certain number of cases of hypertension. It has seemed to me that this occurs mainly in patients who have or have had retinitis. In this event no doubt the lesion represents the emigration of leukocytes from the vessels in the neighborhood of infarcts or of areas of edema of the retina. However, it may be possible that the lymphocytic cuffing that Dr. Rosenberg found about the arterioles at a distance from the infarcts in certain brains may explain the localized periarteriolar sheathing in some cases in which existence of retinitis, past or present, cannot be definitely demonstrated.

With reference to vasospasm and destructive changes, transient loss of vision in one eye or in a sector of an eye does occur at times presumably on the basis of arteriolar spasm. In such cases, when seen during the attack, the main arteriole leading to the affected quadrant is invisible since it is empty of blood, and its walls, being of normal thickness and structure, are invisible or transparent. In such cases, the loss of vision never lasts for more than five minutes. If the loss of vision persists for a period longer than five minutes, an ischemic infarct of the affected portion of the retina can be seen ophthalmoscopically and vision is permanently reduced to a greater or lesser degree, usually greater. In some of these cases, after subsidence of the acute picture of the infarct, the arteriole can be seen to be definitely thrombosed. In other instances, however, the arteriole shows only generalized narrowing, irregularities in lumen and evidence of thickening of the walls, which can be spoken of as postspastic sclerosis. It is certain that in these instances there is a "destructive" lesion in the retina (an infarct with necrosis?), but it is not known whether there is necessarily primary thrombosis of the arteriole or whether the thrombosis, when present, or the residual structural changes in the walls of the arterioles are secondary to the vasospasm, as is the infarct.

In the more usual type of "spasm" of the retinal arterioles, seen for example in toxemia of pregnancy, retinitis does occur in the absence of ophthalmoscopically demonstrable structural changes in the walls of the main arterioles—the visible localized "angiospastic" narrowings at times disappearing and leaving an apparently normal arteriolar wall within twenty-four hours. However, on microscopic study it is possible to demonstrate in certain instances the closure of minute arterioles (20 microns or less in diameter) leading to the region of the cotton wool patch, or infarct (Friedenwald, J. S.: The Pathology of the Ocular Changes in Nephritis and Hypertension, in Berglund, H., and Medes, G.: The Kidney in Health and Disease, Philadelphia, Lea & Febiger, 1935, pp. 638-664), and the question arises, as it does regarding the brains that Dr. Rosenberg examined, whether such a small vascular occlusion must be present in the case of all infarcted foci or whether the apparent infarct or necrosis can be produced by the anoxemia of the tissues attributable to the spasm alone. In the case of the retinal infarcts, Friedenwald concluded that the occlusive changes in the terminal arterioles were due to hyaline lipoid degeneration rather than to thrombosis."

RELATION OF SYMPTOMS TO LESIONS

The histories of the 17 patients with malignant hypertension have been reviewed in an attempt to correlate the cerebral symptoms that were suffered during life with the type of pathologic changes encountered in the brain at autopsy.

In his book published in 1915 Allbutt [34] carefully considered the cause of transient or "larval" forms of cerebral episodes which occur in association with hypertension. He was well informed on the literature dealing with these attacks, and after marshaling the evidence for the functional hypothesis (vasospasm) and for the organic origin, he was obliged to assume that in the vast majority of cases transient pareses in persons with hyperpiesia and chronic renal disease signify small cerebral hemorrhages.

Oppenheimer and Fishberg [35] reviewed the subject of the acute episodes of cerebral phenomena that occur in association with various hypertensive states and independent of uremia. Although at that time they did not report any studies of their own pathologic material, they stated that anatomic examination of the brain of a person who has succumbed after having had these acute manifestations does not reveal any focal lesions to account for the epileptiform convulsions and other symptoms, such as coma, headache, amaurosis, hemiplegia and aphasia, which are so striking during life. They stated that such brains show only inconstant edema or anemia, and because of the paucity of anatomic changes they felt it necessary to seek the pathogenesis of "hypertensive encephalopathy" (as they named the condition) along functional lines. They concluded that the syndrome is due primarily to hypertension and that vasospasms are directly responsible. They were in agreement with Volhard and Fahr,[1] who asserted that these phenomena are not due simply to renal insufficiency.

It would seem apparent from the literature that undoubtedly there have been cases of hypertension in which cerebral symptoms were present during life and in which at necropsy no actual focal lesions could be demonstrated. However, in this study of the brain in malignant hypertension, it was always possible to demonstrate regions of cerebral destruction when focal cerebral symptoms had been present during life, and in instances in which the brain showed no destructive lesions (cases 5, 10 and 14) the history revealed that episodic focal cerebral symptoms

34. Allbutt, T. C.: Diseases of the Arteries, Including Angina Pectoris, London, Macmillan & Co., 1915.

35. Oppenheimer, B. S., and Fishberg, A. M.: Hypertensive Encephalopathy, Arch. Int. Med. **41**:264-278 (Feb.) 1928.

had not been present during life. The present study indicates that when focal cerebral symptoms occur during the terminal illness destructive lesions in the brain are frequently present. A recent paper by Davison and Brill [36] gives emphatic support to this observation.

The case reported recently by me in collaboration with Drs. Keith and Wagener [29] is of special interest in this connection. Severe hypertension developed. The course of the disease was rapid, and the terminal phase was so violent as to be termed by us "explosive." During the final days of the illness there were many bizarre symptoms and findings which appeared to be evidence of a cerebral disturbance. At the time of our original studies, we found no destructive lesions in the brain. We have, however, recently reviewed this case thoroughly in the light of pathologic observations in the present series. In studying many more microscopic preparations from various cerebral regions, we have encountered three exceedingly minute microscopic foci of infarction, but no other lesions. It seems to us that one would not be justified in attributing the many striking cerebral symptoms to these minute lesions.

A PROPOSED CLINICOPATHOLOGIC CLASSIFICATION OF THE CEREBRAL PHENOMENA OF SEVERE HYPERTENSION

After a review of the clinical and pathologic data at my disposal, it appears that three primary types of cerebral symptoms occur in malignant hypertension: (1) symptoms of increased intracranial pressure, (2) symptoms of multiple miliary cerebral lesions and (3) symptoms of large cerebrovascular accidents. Symptoms of any one of these three groups may occur alone, and all combinations of them are seen. Accordingly, a fourth group, mixed types, may be distinguished.

Increased Intracranial Pressure.—The symptoms that result from intracerebral and extracerebral edema are those of increased intracranial pressure and include severe headaches, nausea and vomiting, mental dulness and drowsiness. At necropsy more or less severe arteriolar thickening and narrowing of the lumen of the vessels were noted in these instances of edema, but no destructive lesions of the brain tissue could be found. This simple type occurred in 2 cases (5 and 14) in my group. The following case history is typical.

CASE 14.—A housewife, aged 41 years, was first seen in May 1935, when high blood pressure was discovered. At that time she complained of severe, migraine-like headaches and blurring of vision on stooping. Physical examination revealed

36. Davison, C., and Brill, N. Q.: Essential Hypertension and Chronic Hypertensive Encephalopathy (a Clinico-Pathologic Study), Ann. Int. Med. **12**:1766-1781 (May) 1939.

accentuation of the aortic second sound. At that time her blood pressure was recorded on several occasions as follows: 220 systolic and 125 diastolic; 184 systolic and 120 diastolic, and 196 systolic and 120 diastolic. Examination of the fundus showed retinal arteriolosclerosis of grade 1 to 2 on a basis of 1 to 4, slight generalized narrowing and one small streak hemorrhage below the right disk. The urine did not contain albumin or casts. During the succeeding year the patient was seen occasionally because of spells of faintness, shortness of breath and precordial pain. The blood pressure was always found to be elevated.

On April 16, 1936, she was admitted to the hospital. Her condition was serious. There were marked shortness of breath and a sense of substernal pressure. She had been vomiting frequently for three weeks, had been having frequent nosebleeds and was extremely weak.

Examination revealed a peculiar pallor, which was interpreted as being due possibly to vasospasm of the arterioles of the skin. There were narrowing of the retinal arterioles, grade 2 plus, and sclerosis, grade 3. There was edema of the upper nasal margins of both disks, with an elevation of 1 D. Many hemorrhages were present in the retina of the right eye. Edema was present over the sacrum, and there was evidence of fluid in both pleural cavities. The heart was enlarged. There was marked tenderness over the liver. Severe hypertension was present and continued to within a few days of death (fig. 1).

The urine contained albumin, grade 3. The level of blood urea was 64 mg. per hundred cubic centimeters. The value for hemoglobin was 10.7 Gm. The erythrocytes numbered 3,530,000 and the leukocytes 10,500 in each cubic millimeter of blood. A roentgenogram of the chest revealed enlargement of the heart, passive congestion and fluid at the bases of both lungs. The electrocardiogram showed left ventricular preponderance and inverted T waves in derivation 1. T waves in derivation 2 were isoelectric.

During the succeeding days progressive evidence of renal and cardiac insufficiency developed. In the hospital the patient had severe headaches, often accompanied by nausea and vomiting. A lumbar puncture was performed, the initial pressure being 8 cm. of water and the response to pressure over the jugular veins being prompt. The cell count was 2 per cubic millimeter. The value for proteins in the fluid was 30 mg. per hundred cubic centimeters. It was necessary to remove fluid from both pleural cavities on several occasions. On May 15, 1936, the patient was stuporous. On the following day Cheyne-Stokes respirations were present, and she was in a state of semicoma. The reflexes remained equal on the two sides, and there was no evidence of paralysis. On May 20 a pericardial friction rub disclosed the presence of pericarditis. During the next month her state of consciousness varied; at times she was fairly clear mentally; often she was stuporous. Coma was present for about twenty-four hours before death, which occurred on June 22.

From the time of onset of the symptoms until death only thirteen months had elapsed. At the time of death, the value for blood urea had risen to 192 mg. per hundred cubic centimeters; for creatinine it was 4 mg. and for serum sulfates it was 12.2 mg. At autopsy the following significant diagnoses were made: hypertrophy of the heart (530 Gm., normal 275 Gm.); dilatation of the left ventricle, grade 2 plus; atrophy of the kidneys (237 Gm., normal 275), of arteriolosclerotic type; multiple infarcts and abscesses of the lungs with organized thrombosis of the pulmonary vessels and unresolved bronchopneumonia; hydrothorax (1,000 cc. right side, 2,000 cc. left side); ascites (200 cc.); edema of the legs, grade 2; resolving fibrinous pericarditis, and arteriosclerosis of the aorta, cerebral arteries and coronary arteries—all grade 1.

The brain weighed 1,230 Gm. Beneath the dura, in the epiarachnoid space, were several regions of petechial hemorrhage, each surrounded by a narrow zone of brownish pigment. The brain appeared to be definitely edematous. Arteriosclerosis of the vessels at the base of the brain was graded 1.

There was microscopic evidence of edema of the brain, and small capillary hemorrhages were present in a section from the parietal cortex. Infarctions were not encountered in either the gross or the microscopic examination. Several small vessels were surrounded by dense collections of glial cells. Rather marked medial thickening was encountered in the arterioles of the cortex, but the vessels of the meninges and those of the medulla and the hypothalamus appeared to be only slightly thickened. The internal elastic lamina also appeared to be slightly thickened. Determinations of the ratio of the lumen to the wall of the cerebral arterioles showed reduction only in the cortical vessels.

Marked cardiac and some renal insufficiency developed in a 41 year old woman with severe hypertension. For one month before death she was in a peculiar mental state varying constantly between stupor, semicoma and mental alertness. At times she could obey only simple commands. At other times she was in control of her senses. These symptoms, together with headache, nausea and vomiting, suggested that increased intracranial pressure was present, probably due to edema of the brain. In spite of these clinical phenomena, and in spite of the fact that definite edema of the brain was observed at autopsy, lumbar puncture showed normal pressure readings of the cerebrospinal fluid during life. The outstanding lesion in the brain at autopsy was edema.

Multiple Miliary Destructive Lesions.—When the brain has suffered widespread multiple miliary infarctions or hemorrhages or both, a wide variety of symptoms results; usually these symptoms are evidence of injury to localized cerebral regions. The region of the brain which is destroyed or injured often is not large enough to cause disturbances in reflexes or in sensations or motor power, and the results of neurologic examinations are accordingly usually found to be objectively negative. In 1 instance of this type there occurred episodes of vertigo and staggering, suggesting damage to the equilibratory system; in another, olfactory hallucinations occurred, suggesting injury to a region of the hippocampus. Transient hemiplegias and aphasias are not infrequent, and these suggest lesions in the great projection systems of the cortex. Personality changes suggest damage to the frontal lobes. The observation of many small cortical lesions provide an explanation for the occurrence of convulsions in some of these cases. Cases 2 and 3 represent fairly simple examples of this second type, in which symptoms of focal cerebral disturbance are associated with multiple small destructive lesions of the brain. Case 3 is presented.

CASE 3.—A musician, aged 50 years, came to the Mayo Clinic on Jan. 27, 1927, complaining of shortness of breath for four months. Swelling of the ankles and distention of the abdomen had been present for two weeks.

Examination showed orthopnea and enlargement of the heart. There was accentuation of the pulmonic second sound. Peripheral arteriosclerosis was graded 2. There were ascites and edema of the lumbosacral regions and of the legs. Rales were heard over the bases of both lungs. Results of the gross neurologic examination were negative. Examination of the fundi revealed sclerosis, grade 2, of the retinal arteries, with flame-shaped hemorrhages and numerous cotton wool exudates characteristic of the retinitis of malignant hypertension. Edema of the optic disks was present, with elevation of 1 D. The blood pressure was 220 mm. of mercury systolic and 140 mm. diastolic.

There was a trace of albumin in the urine. The concentration of hemoglobin (Dare) was 72 per cent; erythrocytes numbered 4,000,000 and leukocytes 16,800 in each cubic millimeter of blood. The blood urea measured 124 mg. per hundred cubic centimeters and the creatinine 5 mg. The electrocardiogram showed inversion of the T wave in all three leads.

Two days after the patient's admission to the hospital a severe generalized convulsion suddenly developed, during which he bit his tongue. For a short time he was pulseless and in deep coma; the pulse then returned but for some minutes was rapid and of poor quality. During this period his respirations were stertorous. Venesection was performed, during which procedure he roused and became perfectly rational, talked and moved all extremities. One and a half hours later he had another generalized convulsion. After the second convulsion a Babinski sign could be elicited in the left foot, but tendon reflexes were equal on the two sides and no paralyses were noted.

In the succeeding weeks the patient had periods of marked restlessness with a peculiar personality change. He refused to follow instructions, insisted on getting out of bed, stole ice and water from other patients and drank the water intended for washing his teeth. During the next month edema and ascites increased.

On March 6 he became comatose and died. At the time of death the blood urea was 158 mg. per hundred cubic centimeters and the creatinine 5.3 mg.

At autopsy the following significant diagnoses were established: hypertension with hypertrophy of the heart (870 Gm.), hydrothorax of the left cavity (1,000 cc.) and chronic diffuse nephritis.

Atherosclerosis in the vessels at the base of the brain was graded 3. On sectioning the brain, there were seen many small, scattered regions of hemorrhage (the largest of which was 1.5 cm. in diameter) and numerous small regions of infarction, some of which had formed cavities or cysts. The largest infarct was 8 mm. in diameter.

Microscopically, a mild degree of thickening was noted in the arteries and arterioles of the subarachnoid space. In the parenchyma of the brain proper the walls of most of the arterioles were also definitely thickened. Some arterioles were entirely obstructed by thrombi, and a canalized thrombus was observed in one of them. Many of the cerebral arterioles showed well marked cuffing with lymphocytes. The regions of infarction were noted to be of various ages; many showed scavenger cells and blood pigment. Swollen astrocytes were noted in the vicinity of some infarcts, and about these the adjoining brain tissue was densely infiltrated with various glial cells. Occasional minute capillary hemorrhages were present.

The internal elastic lamina of arterioles was in many instances proliferated and thickened, giving the picture of so-called elastosis, with many fibers of elastic tissue infiltrating and ramifying in the various layers of the wall. Capillary hemorrhages were found in the hypothalamic region, in the cortex and in the medulla.

A man aged 50 years had severe hypertension and heart failure. During the last months of his life he had convulsions, periods of coma and of marked restlessness and personality changes, followed by delirium and terminal coma. In the brain were observed multiple regions of destruction due to hemorrhages and infarcts.

Large Cerebrovascular Accidents and Mixed Types of Cerebral Symptoms.—The phenomenon of a large cerebrovascular accident is well known and deserves no special comment here, except to state that such an accident may follow in the course of either of the aforementioned varieties of clinical course. Thus, a patient the course of whose illness indicated that he has suffered multiple focal destructive cerebral lesions may suddenly show evidences of a large cerebrovascular accident and die. The following case is illustrative of such a course.

CASE 1.—A woman 45 years of age registered at the Mayo Clinic on Aug. 26, 1921. Six months previously she had had a "stroke," followed by partial paralysis of the right side, at which time her systolic blood pressure was 280 mm. of mercury. Paralysis cleared gradually. For two months vision had been failing. She had lost 75 pounds (34 Kg.). For two weeks she had had acute attacks of tinnitus and had noted impairment of memory and vertex headaches. Her mental state was clouded. Since her first stroke she had been emotionally unstable and had expressed many ungrounded fears. Examination showed dyspnea and edema of the ankles. The heart was enlarged. Its action was regular. The aortic second sound was accentuated. The results of the gross neurologic examination were negative. Peripheral arteriosclerosis was graded 2. The blood pressure was 240 mm. of mercury systolic and 120 mm. diastolic.

There were several small conjunctival hemorrhages in the right eye. Papilledema was present, with an elevation of 1 D. in the left eye and 3 D. in the right eye. There were sclerosis of the retinal arteries and irregular narrowing of their caliber. Massive exudates and extensive hemorrhages were noted along the vessels, and beginning macular stars were observed.

The urine contained only a trace of albumin and occasional casts. The concentration of hemoglobin (Dare) was 82 per cent; erythrocytes numbered 5,110,000 and leukocytes 13,000 in each cubic millimeter of blood. The value for blood urea was 34 mg. per hundred cubic centimeters, and that for creatinine 1.9 mg. The specific gravity of urine varied from 1.000 to 1.026.

On the third day after admission the patient suddenly became unable to speak, and left hemiplegia appeared. She lapsed into coma; Cheyne-Stokes respirations developed, and she died two days later.

At autopsy the following significant diagnoses were made: cerebral hemorrhage, chronic diffuse nephritis, hypertrophy of the heart (400 Gm., normal 250 Gm.), early bronchopneumonia and chronic passive congestion of the lungs.

Grossly, the right hemisphere of the brain presented a large cavity, 2 by 5 cm. in diameter, involving the corpus striatum and the internal capsule. This cavity was filled with blood, and blood had ruptured into the ventricles. Scattered about the surface of the cerebrum and cerebellum were numerous hemorrhages beneath the pia. There was sclerosis, grade 2 to 3, of the large vessels at the base of the brain. No gross evidence of infarction was noted.

Microscopic examination showed that the wall of the large hemorrhagic cavity was not organized. The cerebral hemorrhage had obviously occurred within a few hours preceding death.

Sections from the parietal regions of the cortex, from the hypothalamus and from the region of the pons showed numerous small regions of infarction. These were too small to have been seen grossly, but those in the brain stem might easily have interrupted important fiber tracts. Many of these minute infarcts were old, perhaps having occurred some months before death. This fact was shown by the presence of degenerated blood pigment in the walls of the cavities and in the adjoining brain tissues.

There was marked thickening of the arteriolar walls in many of the regions studied.

A 45 year old woman came to the clinic with a history of transient partial hemiplegia of six months' duration. She had been in a peculiar mental state and had many bizarre symptoms, including emotional instability, tinnitus and impaired memory. In spite of this history, the objective results of a careful neurologic examination were negative. A large cerebral hemorrhage caused her death. At autopsy, in addition to the large hemorrhage, multiple minute regions of destruction were observed throughout the brain.

A further variety of the mixed type which may be encountered is exemplified in the following history of a patient the course of whose illness suggested that widespread miliary destructive lesions had occurred and who showed terminal clinical evidence of edema of the brain in the form of signs of increased intracranial pressure.

Case 9.—On July 5, 1934, a physician, 54 years of age, came to the clinic complaining of a loss of weight of 38 pounds (17.2 Kg.) and of malaise and drowsiness, together with marked thirst and polyuria, of about nine months' duration. Two months before his arrival he had experienced olfactory hallucinations, and since that time he had had bouts of nausea and vomiting. He had noted some shortness of breath on exertion, and during the preceding two months severe parietal headaches and insomnia had been very troublesome. He had become mentally dull, and for one month his vision had been failing. During this month he had had visual and auditory hallucinations. He complained of seeing grotesque objects and of hearing voices.

On examination he appeared anemic. Palpable peripheral vascular sclerosis was graded 3 plus. The heart was enlarged, and the aortic second sound was accentuated. The blood pressure varied between 160 and 210 mm. of mercury systolic and 110 and 140 mm. diastolic. The retinal arteries were narrowed and sclerosed. There was retinitis, characterized by the presence of hemorrhages and cotton wool exudates. The nasal margin of the right disk was edematous.

The urine contained albumin and occasional casts, together with erythrocytes and a few pus cells. The value for hemoglobin was 14.5 Gm. per hundred cubic centimeters; erythrocytes numbered 3,830,000 and leukocytes 7,000 in each cubic millimeter of blood. Blood urea was 98 mg. per hundred cubic centimeters and creatinine 2 mg. The electrocardiogram showed left ventricular preponderance and inverted T waves in lead I. T waves in lead II were diphasic.

In the hospital the patient continued to be nauseated and vomited a great deal. Cheyne-Stokes respiration appeared. He became more confused and was troubled by disturbing dreams and thoughts. A gallop rhythm developed; the heart beat became irregular, and rales appeared in the bases of the lungs. The liver was enlarged. The patient became stuporous, slipped into coma and died on Aug. 7, 1934. His blood pressure remained above 200 systolic and 130 diastolic until the day before death. At the time of death the urea of the blood had risen to 144 mg. per hundred cubic centimeters and the creatinine to 5.2 mg. Thus, clinically he presented a picture of terminal cerebral, retinal, cardiac and renal failure.

At necropsy the following significant diagnoses were made: cardiac hypertrophy (651 Gm., normal 300 Gm.); granular kidneys; infarcts of the brain; arteriosclerosis of the aorta, grade 2 plus; edema and congestion of the lungs, and organized bronchopneumonia.

The brain weighed 1,640 Gm. Gross examination revealed flattening of the convolutions, due to edema. Sclerosis of the large cerebral vessels was graded 3. On sectioning the brain numerous small infarcts were seen throughout the white matter of the cerebrum and in the basal ganglions. These measured from 2 to 5 mm. in diameter.

Microscopic examination revealed multiple miliary infarctions throughout the brain. These were found in various sections of the cortex, in the white matter and in the basal nuclei. The infarcts varied in age; fresh infarcts were associated with many scavenger cells and degenerating nerve cells, older ones with many gemästete astrocytes and fewer scavenger cells. Infarcts were found with glial fibers only where brain tissue had been replaced; these were obviously very old. Some infarcts took the form of small cystic cavities with much old blood pigment deposited in the walls. Small capillary hemorrhages were encountered in the arachnoid and in some sections of the cortex. In sections from the frontal cortex dense collections of astrocytes and marked glial fibrosis were observed. Numerous arterioles in these regions showed cuffing with lymphocytes. Many nerve cells in the frontal lobes were degenerated, and around these cells were collected large numbers of oligodendroglial cells. There was definite microscopic evidence of edema. It was believed that the increase in weight of the brain was due in part to the edema and in part to the gliosis.

The arterioles throughout various sections of the cerebral cortex showed moderate thickening of walls, due to increase in size and number of cells of the media—medial hypertrophy. Some vacuolar change was observed in the medial coat of a few arterioles. No other evidence of degeneration or necrosis was seen in the arterioles in any sections examined.

Severe hypertension developed in a 54 year old physician. During the last three months of his life severe symptoms of increased intracranial pressure and cerebral damage appeared in the form of violent headaches, mental dulness, olfactory, visual and auditory hallucinations and, finally, confusion, disturbing thoughts, terminal stupor and coma. At no time during life was any evidence of paralysis noted, and convulsions did not occur. At autopsy, arteriolar changes were only moderately advanced in the cerebral cortex, and slight degrees of thickening were observed in the basal ganglions and brain stem. The brain was unusually heavy, probably owing to edema and gliosis of the

cerebrum. An indeterminate amount of the cerebral substance was entirely destroyed by small macroscopic and countless microscopic infarctions of varying ages.

COMMENT

Seventeen brains from patients who had died of malignant hypertension have been surveyed as a basis for this study. Destructive cerebral injuries were noted in 12 brains, or 71 per cent, a remarkably high incidence. As a result of comparison of the clinical data and the lesions in the brain noted at autopsy, it appears that the cerebral syndromes that occur in patients with malignant hypertension may be divided into various types. For each type characteristic pathologic changes are found. The primary types of cerebral lesion responsible for symptoms appear to be (1) intracerebral and extracerebral edema; (2) multiple miliary destructive lesions, that is, hemorrhages or infarcts or both, and (3) large destructive lesions. In the interest of more exact diagnosis and better understanding of this neurologic phase of hypertension, some such classification should be attempted for every patient with hypertension presenting symptoms of cerebral disturbance.

In the past many of the clinical phenomena occurring in these patients were attributed to spasm of cerebral vessels. These spasms may indeed occur and perhaps are responsible for the lesions. However, it would appear that such an assumption may lead the clinician to an unjustified sense of security concerning the brain. A history of focal cerebral symptoms in these cases of malignant hypertension was found to be associated constantly with more or less widespread cerebral destruction when the brain was examined carefully after death. This study would seem to indicate that in the future those who maintain that these symptoms occur in the absence of destructive lesions must examine the brain carefully. Rosenblath [37] offered an explanation for the occurrence of these symptoms in episodes. He expressed the opinion that each attack is due to the occurrence of one or more new foci and perhaps to increase in size of the original ones. In the light of the observations in my own review, the latter suggestions appear to be tenable.

CONCLUSIONS

1. The cerebral arterioles are profoundly altered in patients with malignant hypertension. The alteration takes the form of an increase in the thickness of the walls with reduction of the caliber of the lumens, such as has been found in many other viscera of patients with this disease.

37. Rosenblath: Ueber die apoplektiforme, nicht embolische und verwiegend unblutige Hirnerweichung und über "Arterio-Capillary Fibrosis" Ztschr. f. klin. Med. **106**:482-527, 1927.

2. The brain is frequently seriously injured by vascular lesions in patients with malignant hypertension.

3. Patients with malignant hypertension whose clinical course suggests that cerebral injury has occurred can be divided into distinct groups on the basis of the nature of these symptoms, and for each group a characteristic pathologic picture can be inferred with considerable accuracy.

4. Transient cerebral phenomena of malignant hypertension that have previously been designated by terms such as "cerebral crisis" or "hypertensive encephalopathy" and ascribed to vasospasm may often be associated with widespread destructive cerebral lesions.

RENAL INFARCTION

STATISTICAL STUDY OF TWO HUNDRED AND FIVE CASES AND DETAILED REPORT OF AN UNUSUAL CASE

HAROLD J. HOXIE, M.D.
AND
CHARLES B. COGGIN, M.D.
LOS ANGELES

Despite the fact that renal infarction has been thoroughly studied experimentally [1] and described in detail from the pathologic and clinical points of view,[2] it has rarely been diagnosed correctly during life. This is because in the majority of cases there are no symptoms. When clinical symptoms and signs do appear, they are alarming and produce difficulties in differential diagnosis which may result in the performance of unnecessary surgical procedures.

We have recently observed an unusual case of renal infarction with hemoglobinuria and uremia. This has stimulated us to review a group of autopsy records.

STATISTICAL STUDY

Review of the protocols of 14,411 autopsies performed at the Los Angeles County Hospital during the past nine years revealed that renal infarcts were present in 205 patients, an incidence of 1.4 per cent. The tiny pitted scars characteristic of renal arteriosclerosis were not included as infarcts. The presence of renal infarcts was diagnosed clinically in only 2 of the patients.

The ages of the patients ranged from 4 months to 88 years. Five of the patients were infants less than 1 year of age. One eighth of the patients were under 30 years of age, and a little more than half were over 50. The ratio of males to females in the group did not differ significantly from that in the entire series.

From the Department of Medicine of the College of Medical Evangelists and the Los Angeles County Hospital.

1. Karsner, H. T., and Austin, J. H.: Studies in Infarction, J. A. M. A. **57**:951-958 (Sept. 16) 1911.

2. (*a*) Desjacques, R., and Boijeau, A.: Les gros infarctus du rein, Lyon chir. **33**:645-674 (Nov.-Dec.) 1936. (*b*) Schildt, E.: Ueber den aseptischen, embolischen Niereninfarkt, Acta chir. Scandinav. **70**:299-352, 1933. (*c*) Lemierre, A.: Sur un cas d'infarctus rénal, Prat. méd. franç. **13**:711-724 (Oct., B) 1932. (*d*) Barney, J. D., and Mintz, E. R.: Infarcts of the Kidney, J. A. M. A. **100**:1-6 (Jan. 7) 1933. (*e*) Danhiez, P.: Les grands infarctus rénaux, J. d'urol. **23**:481-495 (June) 1927. (*f*) Folsom, A. I., and Alexander, J. C.: Total Infarction of Right Kidney: Fibrotic Atrophy of Left Kidney; Case Presentation, Urol. & Cutan. Rev. **38**:197-198 (March) 1934. (*g*) Schwartz, J.: Renal Infarcts: Surgical Aspect of Bacterial Endocarditis, Am. J. Surg. **39**:70-76 (Jan.) 1938. (*h*) Aschner, P. W.: The Clinical Importance of Aseptic Infarction of the Kidney, Am. J. M. Sc. **164**:386-401 (Sept.) 1922.

Ninety per cent of the patients were admitted to medical services; only 4 were admitted to the urologic service. This is in accord with the fact that the causative lesion is usually in the heart. In 76.6 per cent of the 205 patients definite cardiac lesions were present. Furthermore, of 242 patients with bacterial endocarditis in the entire series of 14,411 autopsies, 55, or 22.7 per cent, had embolic infarction of the kidneys.

The causes of occlusion of the renal vessels are recorded in table 1.

Four of the five infants had thrombosis of a renal vein with infarction of an entire kidney. All four infants were emaciated and dehydrated incident to an acute infectious disease or malnutrition. Marshall and Whapham [3] reported bilateral renal infarction in an infant, who died twenty days after the onset. No definite cause was found for the infarction.

TABLE 1.—*Sources of Embolism or Thrombosis of the Renal Vessels*

	Cases
Rheumatic heart disease with	
Fibrillation and subacute bacterial endocarditis	3
Fibrillation without subacute bacterial endocarditis	27
Subacute bacterial endocarditis but no fibrillation	29
Neither fibrillation nor subacute bacterial endocarditis	1
Presence or absence of fibrillation not known	4
Coronary occlusion with mural thrombi	29
Coronary occlusion without mural thrombi	6
Sclerosis of aorta or renal arteries	24
Acute bacterial endocarditis	20
Pulmonary disease (empyema, infarcts, pneumonia)	7
Auricular fibrillation with intracardiac thrombi	7
Auricular fibrillation, no thrombi found	4
Hypertensive heart disease without auricular fibrillation	3
Intracardiac thrombi, cause not found	6
Syphilitic heart disease	1
Syphilitic aortitis with bacterial vegetations *	3
Venous thrombosis	4
Aneurysm of aorta	3
Septicemia and pyemia	3
Periarteritis nodosa	1
Not known	20

* These cases were reported by H. E. Martin and W. L. Adams Jr. (Am. Heart J. **16**: 714 [Dec.] 1938).

Seventy-three patients had only one renal infarct each. Two infarcts were present in each of 25 patients, and three or more in each of 105.

Bilateral infarction was found in 102 patients; infarction was present in the right kidney alone in 42 and in the left kidney alone in 56. These data seem to support the statement by Falci [4] that embolic occlusion is more frequent on the left side because the left renal artery forms an acute angle with the aorta.

No statement of the age of the infarcts was made in the records of 21 patients. The infarcts in 65 patients were classified as pale; those in 27, as both red and pale; those in 41, as red or recent, and those in 15, as both scars and recent infarcts. In 36 patients only scars were present in the kidneys. The frequency of healed infarcts (25 per cent) demonstrates that renal infarction does not necessarily indicate early death.

3. Marshall, S., and Whapham, E.: Case of Bilateral Renal Infarction in Newly Born Infant, Lancet **2**:428-429 (Aug. 22) 1936.

4. Falci, E.: Sur la nécrose du rein, J. d'urol. **18**:449-465 (Dec.) 1924.

The size of the infarcts was not stated in 69 records. They were less than 1 cm. in diameter in 25 patients and between 1 and 2 cm. in 55. Thirty were classified as large and 22 as small. One third of a kidney was infarcted in each of 3 patients, one half in 1 patient and an entire kidney or more in each of 9 patients.

Infarcts of other organs were present in 69 per cent of the patients. The spleen contained notable infarcts in 91 instances, the brain in 51 and the lungs in 50. Other organs were much less frequently involved.

In only 117 records was microscopic examination of the urine mentioned, and in most of these it was stated that only one specimen had been examined. The urine of 4 patients was grossly bloody. Thirty-five patients, or about 30 per cent of those whose urine was examined, had hematuria. (These 35 do not include any who had calculi, infection or tumors of the urinary tract.) Twenty-five of the 35 patients also had albuminuria. Albuminuria was recorded for 71 of the 133 patients whose urine was tested.

Sixty-seven per cent of the patients had some degree of fever, but in only 2 was the fever not explained by accompanying lesions. Both of these patients had infarction of an entire kidney or more, and the fever was of moderate degree.

The blood pressure was above 140 systolic and 90 diastolic in 34 per cent of the patients, but in no instance could it be proved that the rise was due to the renal infarction.

In 35 histories it was stated that abdominal or back pain had been inquired about, and in 14 this symptom was recorded as present. In 13 of the 14 patients either large or many small ones were present. The pain was recorded as being on the same side as a unilateral infarct in 3 cases; in 3 other cases it was present on one side and infarcts were found in both kidneys.

Of 44 histories in which tenderness in the costovertebral angle was mentioned, the sign was recorded as present in 14. In 11 of the 14 patients large or many small infarcts were found. In 2 patients the tenderness was on the same side as the unilateral infarcts and in 2 others tenderness on one side was associated with infarcts in both kidneys.

Six patients had nausea and vomiting; the degree of infarction was great in 5 of these.

In the histories of 9 patients mention was made of urinary symptoms not accounted for at autopsy by lesions other than renal infarcts. Nocturia and frequency of urination were each mentioned in 3 histories, dysuria in 2 and oliguria in 1.

Two patients had uremia. Both had extensive infarction of both kidneys.

REPORT OF CASE

At 6 p. m. on Jan. 14, 1938, an unmarried Mexican woman, aged 38, began to have pain in the middle of the back. It was aching in character at first, but within the next two hours it became severe and sharp and spread to the entire upper part of the abdomen. At the onset she had four shaking chills and felt feverish. She became very weak and dyspneic. The pain did not decrease in severity, and she passed no urine until the afternoon of January 16, at which time the pain lessened, and she began to void frequently, each time passing small amounts of bloody urine. There was no pain on urination.

During the three days between the onset of pain and her admission to the hospital she was nauseated and had vomited about twenty-five times—at first food and later clear fluid, but never blood.

The patient had had three attacks of fever, with pain and swelling in the joints, at 6, 16 and 34 years of age. Moderate dyspnea on exertion and occasional palpitation had persisted since the initial attack. Edema of the ankles had been present for the past few years.

Examination.—The patient appeared to be acutely ill. She was moderately dyspneic, and her lips and nails were cyanotic. She was perspiring, and her skin was cold. The veins of her neck were distended and pulsating. Her temperature was 96.8 F.; pulse rate, 120; respirations, 40. The blood pressure was 96 systolic and 74 diastolic. The percussion note was normal over both lungs. There were bronchovesicular breath sounds and crepitant rales in the bases of both lungs posteriorly. The area of cardiac dulness was widened to the left. The apical rate was 174; the rhythm was absolutely irregular. The heart sounds were distant. The pulmonic second sound was accentuated. There was an apical systolic murmur. The abdomen was soft, distended and tympanic. There were tenderness in both costovertebral angles and generalized abdominal tenderness, maximum in the flanks and in the epigastrium. The tendon reflexes were normal. There was no edema.

The leukocyte count was 19,250 on admission.

Approximately 5 cc. of bright red and almost clear urine was obtained by catheter. Benedict's test for sugar was negative. The urine showed coagulation and turned brown with Robert's reagent. Microscopic examination of the uncentrifuged urine showed red blood cells and leukocytes—one or two of each per high power field. When viewed under the spectroscope, the urine presented absorption bands characteristic of oxyhemoglobin.

The clinical impression on admission was rheumatic heart disease, with auricular fibrillation, and massive embolic infarction of the kidneys.

Course.—Oxygen, warm blankets and morphine were used to counteract shock. Nine grains (0.58 Gm.) of digitalis was given intravenously within twelve hours after admission. No more digitalis was given. On the morning after admission the blood pressure was 160 systolic and 106 diastolic. The heart rate was 140; the rhythm was more regular, with only short periods of fibrillation. The same afternoon the heart rate was 70 and the rhythm regular. The next morning the blood pressure was 146 systolic and 78 diastolic; the heart rate was 56 and regular. A loud systolic and a rumbling diastolic murmur were now heard over the area of the mitral valve.

During the forty-eight hours following admission the patient voided only four times, each time passing very small amounts of bright red urine. During the next two days she apparently had complete anuria.

From Jan. 19 until her death on January 21, the patient gradually became irrational. The lungs became more edematous, and rapid changes occurred in the electrocardiogram, which suggested myocardial infarction (fig. 1).

Postmortem Examination.—Autopsy was performed one and one-half hours after death. The weight of the body was 170 pounds (77.1 Kg.); the length, 64 inches (160 cm.).

The heart weighed 400 Gm. The epicardium was covered by a very thin fibrinous exudate, and there were many tiny petechiae over the anterior surface of the apex. All the chambers except the left ventricle were dilated. There was a

smooth thrombus 2 cm. in diameter in the left auricular appendage (fig. 2). The thickness of the wall of the left ventricle was 12 mm., and that of the right ventricle was 5 mm. The mitral leaflets were thickened and adherent and the chordae tendineae were shortened and greatly thickened. The orifice of the mitral valve was of buttonhole appearance and was 6 cm. in circumference. The orifice of the aortic valve was also 6 cm. in circumference, and the thickened leaflets were adherent at the commissures. There were only a few atheromatous plaques in the aorta. The pulmonary artery and its branches were thickened and arteriosclerotic.

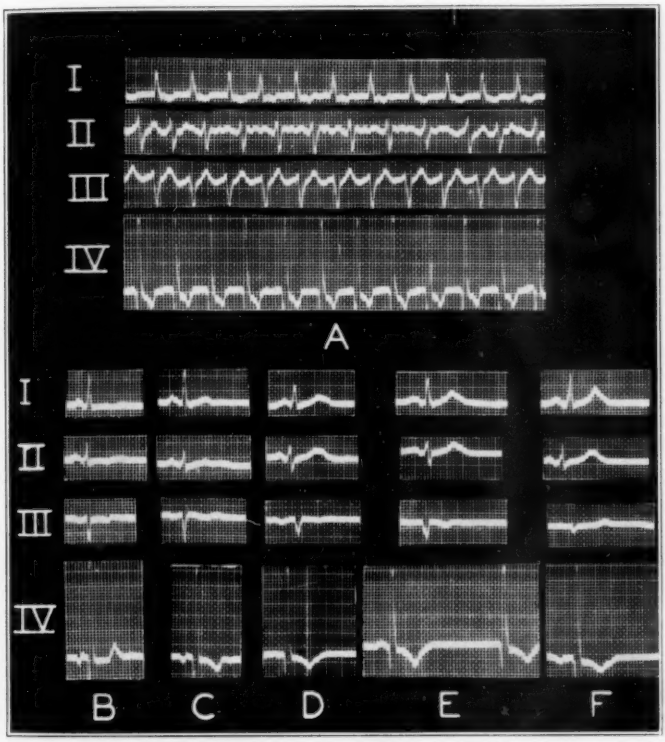


Fig. 1.—These tracings illustrate the rapid changes in the electrocardiograms of the case reported. Lead IV is the precordial lead with the electrode over the apex, the positive deflection being downward. The single complexes from *B* to *F* were cut to include exactly one cardiac cycle. *A*, 10 a. m., Jan. 18; a paroxysm of auricular fibrillation. *B*, 2 p. m., Jan. 18. *C*, about 9 a. m., Jan. 19. *D*, about 9 a. m., Jan. 20. *E*, 2 p. m., Jan. 20. Note sinus arrest with ventricular escape in lead IV. *F*, 9 a. m., Jan. 21, four hours before death.

The lungs, liver, gastrointestinal tract and spleen were normal except for moderate passive congestion.

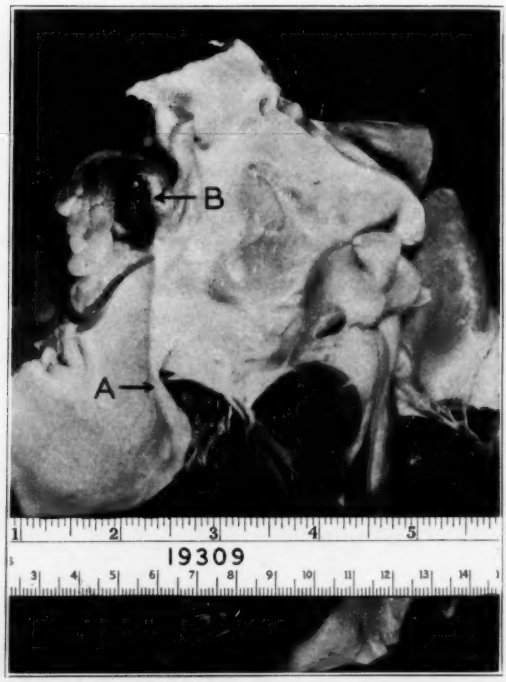


Fig. 2.—Posterior view of the opened left auricle and ventricle. The mitral valve (*A*) is narrowed and the leaflets thickened. The thrombus (*B*) can be seen in the left auricular appendage.

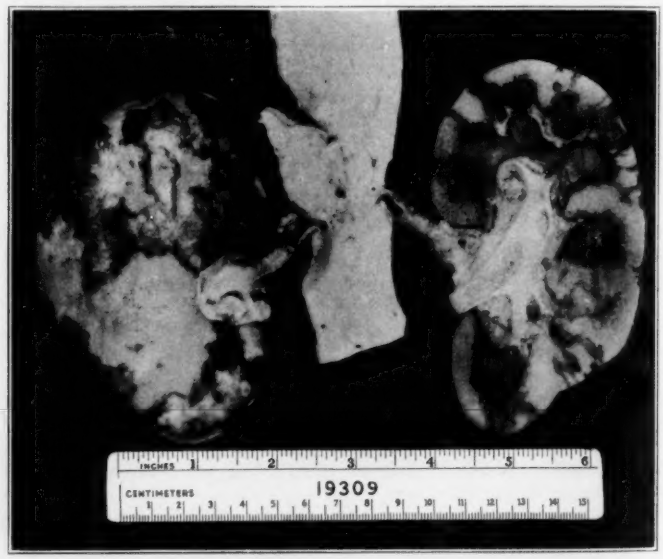


Fig. 3.—Posterior view showing antemortem thrombotic material in both renal arteries. The right kidney has been cut through the pelvis. The dark areas are hemorrhagic and the pale areas necrotic tissue.

The kidneys together weighed 400 Gm. The outer surfaces were mottled by large irregular hemorrhagic areas (fig. 3). The normal markings at the cut surfaces were completely obliterated by large opaque pale areas and by irregular hemorrhagic zones. The renal arteries were both occluded through their entire lengths by loosely adherent antemortem thrombi. The bladder contained bloody urine.

The creatinine content of blood taken at autopsy was 14 mg. per hundred cubic centimeters.

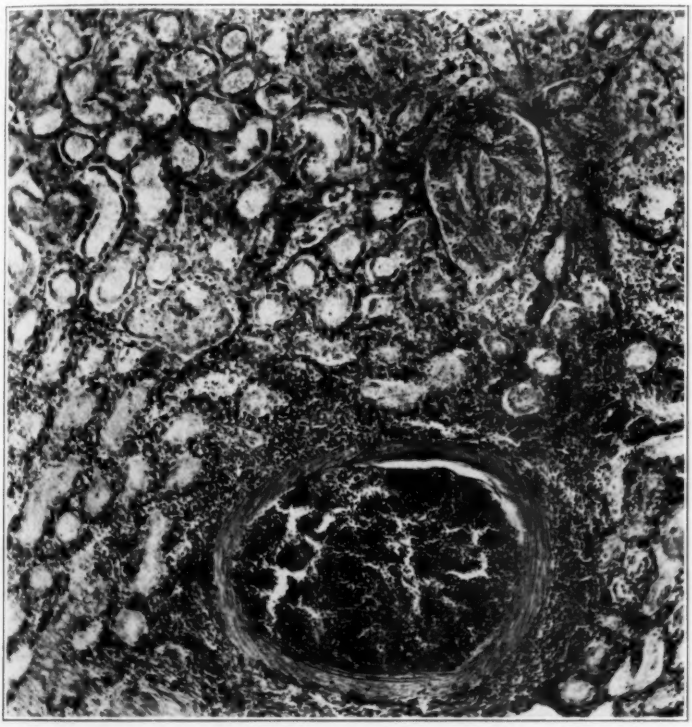


Fig. 4.—Photomicrograph of a section of one of the columns of Bertin. The small artery is thrombosed and the surrounding tissue is infiltrated with red blood cells and leukocytes. The cells of the tubules in this region are not completely necrotic. Hematoxylin and eosin stain; × 105.

On microscopic examination, the heart and spleen appeared normal. The lungs showed minimal bronchopneumonia. In the kidney there was an area of reactive hyperemia below a narrow zone of partially necrotic tubules just under the capsule. Below the area of hyperemia all the tissue was necrotic, except for some viable tubules, filled with hyaline material, in the columns of Bertin. Many of the small veins and arteries were filled with thrombi (fig. 4).

COMMENT

Complete simultaneous bilateral embolic occlusion of the renal arteries must be rare. There are several reports of oliguria, complete anuria and uremia due to extensive renal infarction,[5] but we have not been able to find a report of a case similar to ours.

The changes in the electrocardiograms in the case which we have described resemble those observed by Master, Jaffe and Dack [6] in a case of acute nephritis.

Hemoglobinuria following renal infarction has been mentioned by Danhiez [2e] and lately by Libman and Fishberg.[7] Hemoglobin is liberated in the infarcted area by autolysis. In another case of early infarction of an entire kidney we have been able to demonstrate free hemoglobin in the involved kidney.

SUMMARY AND CONCLUSIONS

A case of complete simultaneous bilateral embolic occlusion of the renal arteries is reported in detail.

In a series of 205 cases of renal infarction the most common causes for occlusion of the renal vessels were bacterial endocarditis, auricular fibrillation with intra-auricular thrombi, coronary occlusion and arteriosclerosis.

Clinical symptoms and signs were frequently absent. When present they were usually associated with extensive infarction. In only 2 cases of the 205 in the series was the diagnosis made ante mortem. It thus appears that clinical diagnosis of this condition is to be based on:

(*a*) Cardiovascular disease; this was noted in a little over four fifths of our material.

(*b*) Emboli in other organs; these were noted in two thirds of our cases.

(*c*) Severe pain in the back, tenderness in the costovertebral angle, urinary complaints, nausea and vomiting.

(*d*) Hematuria and impaired function of the affected kidney, in the absence of other reasonable causes.

The prognosis is usually that of the lesion causing the renal infarction.

---

5. (*a*) Lemierre, A.; Laudat, M., and Laporte, A.: Étude de l'azotémie, de la chlorémie et de la sécrétion urinaire dans un cas d'infarctus rénal: Remarques sur les indications et les effets de la cure de rechloruration, Bull. et mém. Soc. méd. d. hôp. de Paris **48**:1224-1236 (July 18) 1932. (*b*) Lemierre.[2c] (*c*) Folsom and Alexander.[2f]

6. Master, A. M.; Jaffe, H. L., and Dack, S.: (*a*) The Electrocardiogram in Acute Nephritis, Am. Heart J. **12**:244 (Aug.) 1936; (*b*) The Heart in Acute Nephritis, Arch. Int. Med. **60**:1016-1027 (Dec.) 1937.

7. Libman, E., and Fishberg, A. M.: Unilateral Hemoglobinuria: Its Occurrence in Infarction of the Kidney, Ann. Int. Med. **11**:1344-1347 (Jan.) 1938.

DISTURBANCES OF RATE AND RHYTHM IN HYPERTENSIVE HEART DISEASE

NATHAN FLAXMAN, M.D.
Clinical Associate in Medicine, Loyola University Medical School
CHICAGO

The disturbances of rate and rhythm which occur in the course of hypertensive heart disease have been accorded little or no attention to date. Extrasystoles of the ventricular type are considered common, but no figures are available as to their frequency. Of other rhythmic disturbances, White [1] reported that in a group of 708 cases of hypertensive heart disease auricular fibrillation was noted in 92 (13 per cent), paroxysmal tachycardia in 11 (1.5 per cent), auricular flutter in 2 (0.3 per cent) and auriculoventricular block in 13 (1.8 per cent). The incidence of auricular fibrillation has been reported as 2.2,[2] 13,[1] 13.7 [3] and 25.3 per cent.[4]

Arrhythmias other than ventricular extrasystoles, such as auricular flutter, the various tachycardias, nodal rhythm and heart block, have been reported infrequently in series of cases of hypertensive heart disease, since they do not occur commonly in this condition. Nor are reports of individual cases common. Auricular flutter was noted as a result of hypertension in 12 (18.5 per cent) of 65 cases of flutter due to all causes.[5] Isolated case reports of the various tachycardias have emphasized the arrhythmia and not the type of heart disease underlying the disturbance. Textbooks on heart disease make no mention of nodal rhythm or of heart block occurring solely on the basis of the effects of hypertension on the heart.

From the Department of Medicine, Loyola University School of Medicine.

1. White, P. D.: Heart Disease, New York, The Macmillan Company, 1934, p. 396.

2. Janeway, T. C.: A Clinical Study of Hypertensive Cardiovascular Disease, Arch. Int. Med. **12**:755 (Dec.) 1913.

3. White, P. D.: A Note on the Common Occurrence of Serious Involvement of the Heart in Hyperpiesia, New England J. Med. **214**:719, 1936.

4. Flaxman, N.: Auricular Fibrillation: Its Influence on the Course of Hypertensive Heart Disease, J. A. M. A. **108**:797 (March 6) 1937.

5. McMillan, T. M., and Bellet, S.: Auricular Flutter, Am. J. M. Sc. **184**: 33, 1932.

In 1917 Musser [6] reported 2 cases of heart block associated with high blood pressure; aside from the work by Rosenthal,[7] it is the only report of its kind in the literature to date. It is true that the disturbances of rate and rhythm probably occur with the same frequency in the common types of heart disease due to other causes, but they have certain characteristics in hypertensive heart disease which make them different.

ANALYSIS OF MATERIAL

An analysis of the arrhythmias found in 800 cases of uncomplicated hypertensive heart disease is presented in this report (table 1). All types included, the incidence of the arrhythmias was 30 per cent. The following irregularities were observed in 243 patients:

	No. of Patients
Extrasystoles	28
Auricular	6
Nodal	7
Ventricular	15
Auricular fibrillation	198
Auricular flutter	3
Paroxysmal tachycardia	3
Auricular	1
Nodal	1
Ventricular	1
Nodal rhythm	4
Wandering pacemaker	1
Heart block	6

Prolongation of the PR interval (partial heart block), which was observed in 4 (0.5 per cent) of the 800 cases, will be considered in a subsequent article on the disturbances in conduction occurring in hypertensive heart disease. Bundle branch block has been reported on in detail in a previous publication.[8]

In the entire series of 800 patients, the ratio of men to women was 4:1. The same ratio applied to the 243 patients with the arrhythmias. An exception was the group of patients with extrasystoles, in which the ratio of men to women was 27:1.

The combined type of ventricular (congestive heart) failure occurred in 72 per cent of the total number of patients and in 70 per cent of those with arrhythmias, so that the type of hypertensive heart failure, as a rule, made little difference. The mortality in the two

6. Musser, J. H., Jr.: Heart Block Associated with High Blood Pressure, Arch. Int. Med. **20**:127 (July) 1917.

7. Rosenthal, S. R.: Branch Arborization and Complete Heart Block, Arch. Int. Med. **50**:730 (Nov.) 1932.

8. Flaxman, N.: The Course of Hypertensive Heart Disease: III. Significance of Bundle-Branch Block, Ann. Int. Med. **11**:1607, 1938.

groups was about the same, 29 and 27 per cent, so that it was not the more seriously ill patients who had the arrhythmias.

Extrasystoles.—Extrasystoles occurred in 28 (3.5 per cent) of the total number of cases. They were ventricular in 13 cases (table 2), auricular and nodal in 4, nodal and ventricular in 2, auricular in 4 and nodal in 5 (table 3). Multiple extrasystoles were the rule rather than the exception. It has been said that the appearance of frequent

TABLE 1.—*Analysis of Cases of Arrhythmia in 800 Cases of Hypertensive Heart Disease*

	Number of Cases	Incidence, Per Cent	Sex Ratio, M:F	Ventricular Failure: Combined, Per Cent of Cases	Ventricular Failure: Left, Per Cent of Cases	Mortality, Per Cent
Total series	800	...	4:1	72	27	29
Arrhythmias	243	30.4	4:1	70	30	27
Extrasystoles	28	3.5	27:1	67	33	35
Auricular fibrillation	198	24.8	4:1	70	30	25
Auricular flutter	3	0.4	3:0	100	0	33
Nodal rhythm	4	0.5	4:0	50	50	50
Paroxysmal tachycardia	3	0.4	2:1	66	33	33
Complete heart block	6	0.7	2:1	33	66	33
Wandering pacemaker	1	0.1	1:0	100	0	0

TABLE 2.—*Multiple Ventricular Extrasystoles*

Case	Sex	Age	Duration of Symptoms	Ventricular Failure	Size of Heart, Cm.	Heart Rate	Outcome
1	M	53	2 yr.	Combined	20	90	Death, congestive heart failure
2	M	58	3 yr.	Left	18	80	Regular rhythm
3	M	48	1 mo.	Combined	18	90	Regular rhythm
4	M	63	2 wk.	Combined	18	70	Regular rhythm
5	M	37	6 mo.	Combined	23	80	Death, cerebral hemorrhage
6	M	45	1 yr.	Combined	22	82	Regular rhythm
7	M	49	3 mo.	Combined	20	92	Death, congestive heart failure
8	M	72	3 mo.	Combined	18	86	Regular rhythm
9	M	71	6 mo.	Combined	20	110	Death, congestive heart failure
10	M	72	2 yr.	Left	22	100	Regular rhythm
11	M	65	6 mo.	Combined	22	100	Regular rhythm
12	M	63	5 yr.	Combined	22	100	Regular rhythm
13	M	69	2 wk.	Combined	20	120	Regular rhythm

ventricular extrasystoles may be the forerunner of ventricular tachycardia, but this did not occur in my series. Only 2 of the 19 patients with premature ventricular beats had a bigeminal rhythm. No instances of trigeminal or quadrigeminal cycles were noted. The extrasystoles, except in the 2 cases of bigeminal rhythm, arose from multiple foci in the heart muscle. The immediate mortality, 35 per cent, was higher than in the entire series. Ten of the 28 patients with premature beats died while the arrhythmia was present. In 8 (80 per cent) of these 10 cases the cause of death was congestive heart failure; in 1 it was coronary occlusion, and in the other, a cerebral hemorrhage.

In only 3 of the 10 patients who died did the extrasystoles arise not only from multiple foci but also from several sources in the heart (auricle and ventricle in 2 and auriculoventricular node and ventricle in 1), so that this factor did not enter into consideration. The small difference in the mortality and the slightly higher number of deaths due to congestive heart failure in this group than in the entire series did not indicate that premature beats were of great clinical importance in the course of hypertensive heart disease. However, it should be kept in mind that they may be confused with auricular fibrillation, since they tend to be multifocal in origin.

TABLE 3.—*Other Types of Extrasystoles*

Case	Sex	Age	Type of Beats	Duration of Symptoms	Ventricular Failure	Size of Heart, Cm.	Heart Rate	Outcome
1	M	49	Auricular and ventricular	2 mo.	Combined	20	116	Death, congestive heart failure
2	M	65	Auricular and ventricular	3 yr.	Left	23	80	Compensation
3	M	49	Auricular and ventricular	2 mo.	Combined	20	116	Death, congestive heart failure
4	M	65	Auricular and ventricular	3 yr.	Left	23	80	Compensation
5	F	33	Nodal and ventricular	2 wk.	Combined	18	130	Compensation
6	M	75	Nodal and ventricular	5 yr.	Left	15	110	Death, congestive heart failure
7	M	47	Auricular	1 wk.	Left	18	90	Death, coronary thrombosis
8	M	68	Auricular	1 wk.	Left	18	90	Compensation
9	M	74	Auricular	2 mo.	Left	23	88	Compensation
10	M	68	Auricular	1 yr.	Combined	20	100	Compensation
11	M	50	Nodal	1 yr.	Left	18	100	Compensation
12	M	63	Nodal	6 wk.	Combined	23	80	Compensation
13	M	56	Nodal	2 yr.	Combined	17	80	Death, congestive heart failure
14	M	56	Nodal	5 yr.	Combined	18	110	Compensation
15	M	70	Nodal	1 mo.	Combined	18	110	Death, congestive heart failure

Auricular Fibrillation.—In a previous study of the influence of auricular fibrillation on the course of hypertensive heart disease,[4] the incidence was found to be 25.3 per cent. It was noted that the irregularity was not a late manifestation entirely, since it occurred with equal frequency in all groups of patients. The incidence of auricular fibrillation in the present series was approximately the same as in 198 (24.8 per cent) of the 800 patients. The ratio of men to women was again 4:1.

Auricular fibrillation definitely influenced the course of the disease in 54 patients (27.3 per cent) in whom the rapid irregularity preceded and precipitated the congestive heart failure, and in 10 (18.5 per cent) of whom it led to early death from this cause, within one month after the onset. When the auricular fibrillation occurred after congestive heart failure had been present from one month to several years, it had no

apparent influence on the course of the disease except in relation to the cause of death and the comparative absence of additional complications commonly appearing in hypertensive patients.

The lowest mortality, 25 per cent, occurred in patients with auricular fibrillation, mainly because of the rarity of coronary thrombosis. The cause of 45 (81.8 per cent) of the 55 deaths (table 6) was congestive heart failure. Coronary thrombosis caused only 2 deaths among these

TABLE 4.—*Ages of Patients at the Onset of Auricular Fibrillation*

Ages	Men	Women	Total	Per Cent
31 to 40	8	5	8	4.1
41 to 50	43	9	52	26.2
51 to 60	67	16	83	41.9
61 to 70	34	13	47	23.7
71 to 80	6	2	8	4.1
Totals	153	45	198	100.0

TABLE 5.—*Ages of Patients with Auricular Fibrillation at Time of Death*

Ages	Men	Women	Total	Per Cent
31 to 40	0	2	2	3.6
41 to 50	6	1	7	12.7
51 to 60	24	6	30	54.6
61 to 70	10	2	12	21.8
71 to 80	2	2	4	7.3
Totals	42	13	55	100.0

TABLE 6.—*Causes of Death of 55 Patients with Auricular Fibrillation*

Causes	Men	Women	Total	Per Cent
Congestive heart failure	33	12	45	81.8
Uremia	2	1	3	5.5
Cerebral hemorrhage	1	0	1	1.8
Coronary thrombosis	2	0	2	3.6
Miscellaneous	3	1	4	7.3
Totals	41	14	55	100.0

patients with auricular fibrillation. The antagonism between auricular fibrillation and coronary thrombosis is not clear, but it has been noted before by Levine [9] and by Parkinson and Campbell.[10]

Auricular Flutter.—There were 3 patients with auricular flutter, 1 of whom died of congestive heart failure during the attack of the arrhythmia (table 7). The condition in the other 2 was converted to

9. Levine, S. A.: Coronary Thrombosis, Medicine **8**: 245, 1929.

10. Parkinson, J., and Campbell, M.: Paroxysmal Auricular Fibrillation, Quart. J. Med. **23**:67, 1930.

sinus rhythm by means of digitalis and quinidine, but the 65 year old man failed to respond.

Nodal Rhythm.—There were 4 hypertensive patients with nodal rhythm (table 8) and 1 with a wandering pacemaker. The arrhythmias persisted, and 2 of the 5 patients died, 1 of congestive heart failure and the other of coronary occlusion. The heart rate was normal, from 66 to 100, in all 5 patients, and neither digitalis nor quinidine affected

TABLE 7.—*Auricular Flutter*

Case	Sex	Age	Duration of Symptoms	Ventricular Failure	Size of Heart, Cm.	Heart Rate	Outcome
1	M	59	3 yr.	Combined	16	320:160	Condition converted to sinus rhythm
2	M	65	3 yr.	Combined	22	300:100	Death, congestive heart failure
3	M	52	4 mo.	Combined	18	300:150	Condition converted to sinus rhythm

TABLE 8.—*Nodal Rhythm and Wandering Pacemaker*

Case	Sex	Age	Duration of Symptoms	Ventricular Failure	Size of Heart, Cm.	Heart Rate	Outcome
				Nodal Rhythm			
1	M	68	4 yr.	Combined	20	70	Compensation
2	M	56	2 wk.	Left	22	90	Compensation
3	M	62	1 yr.	Combined	20	100	Death, coronary thrombosis
4	M	47	3 mo.	Left	19	66	Death, congestive heart failure
				Wandering Pacemaker			
1	M	38	8 mo.	Combined	21	116	Compensation

TABLE 9.—*Paroxysmal Tachycardia*

Case	Sex	Age	Type of Tachycardia	Duration of Symptoms	Ventricular Failure	Size of Heart, Cm.	Heart Rate	Outcome
1	F	43	Auricular	6 mo.	Combined	18	190	Regular rhythm
2	M	42	Nodal	3 wk.	Left	19	100	Death, uremia
3	M	67	Ventricular	4 mo.	Combined	20	170	Regular rhythm

the nodal rhythm. In those who recovered compensation was effected by use of digitalis, but the rhythm remained governed by the auriculoventricular node. Vischer and Lowell [11] reported a case of auriculoventricular rhythm in a 46 year old man, with decompensation and symptoms of two years' duration; the blood pressure was 210 systolic and 130 diastolic and the cardiac rate 52, but death occurred three days after admission to the hospital.

11. Vischer, C. V., and Lowell, L. L.: Auriculoventricular Nodal Rhythm, Ann. Int. Med. **5**:1010, 1932.

Paroxysmal Tachycardia.—Only 3 instances of paroxysmal tachycardia were noted among the 800 patients, an incidence of 0.4 per cent. The ventricular rates were 190, 100 and 170 for each of the three types: auricular, nodal and ventricular, respectively (table 9). Schwab [12] reported 3 cases of paroxysmal tachycardia, in the first 2 of which the patients had hypertensive heart disease. His second patient had a nodal rhythm and died of uremia. The second patient in my series, a 42 year old man with nodal tachycardia, also died of uremia. Both patients with paroxysmal tachycardia, 1 with the auricular and the

TABLE 10.—*Complete Heart Block*

Case	Sex	Age	Duration of Symptoms	Ventricular Failure	Size of Heart, Cm.	Heart Rate	Outcome
1	M	55	1 wk.	Left	19	70:19	Death during attack of Adams-Stokes disease
2	F	65	6 yr.	Left	18	64:32	Compensation
3	F	41	6 mo.	Combined	19	70:35	Death, congestive heart failure
4	M	70	3 yr.	Left	18	90:45	Compensation
5	M	77	6 wk.	Left	20	84:42	Compensation
6	M	64	1 yr.	Combined	23	90:45	Compensation

TABLE 11.—*Heart Rate in 422 Cases of Hypertensive Heart Disease with Regular Rhythm*

	Normal Rate	Sinus Tachycardia	Sinus Bradycardia
Number of cases	191	222	9
Incidence	45.3%	52.6%	2.1%
Ratio, male : female	4.6:1	2.4:1	9:0
Congestive heart failure	60.7%	80.1%	55.5%
Mortality	20.3%	39.2%	22.2%
Average ventricular rate	61:99	100:150	50:60

other with the ventricular type, recovered with compensation after quinidine had corrected the marked rhythmic disturbance.

Heart Block.—Six hypertensive patients had complete heart block, with ventricular rates between 19 and 45 beats per minute (table 10). Five of the 6 had a 2:1 block. The sixth patient, who had a 4:1 block, with a ventricular rate of 19 beats per minute, died during an attack of Adams-Stokes syndrome one week after the onset of isolated left ventricular failure. Another patient died of congestive heart failure six months after the heart failure and the complete block had appeared. The other patients were alive six weeks, one year, three years and six years, respectively, after the block became established.

12. Schwab, E. H.: Observations on the Etiology and Treatment of Paroxysmal Ventricular Tachycardia, Am. Heart J. **6**:404, 1931.

Association of Arrhythmias.—No combination other than auricular fibrillation associated with bundle branch block was noted among the 243 patients with the arrhythmias. The absence of associated disturbances was probably due to the lack of acute physiologic and pathologic changes in the heart muscle or in its blood supply. This leads to the important consideration that once a permanent arrhythmia develops in the heart of a patient with hypertension other disturbances of rhythm do not appear; for instance, in patients with acute conditions of the coronary arteries,[13] acute changes in the blood supply and in the heart muscle often lead to the occurrence of two or more arrhythmias simultaneously, in close association or in succession.

Normal Heart Rate.—In 191 patients (45.3 per cent of 422 with regular sinus rhythm) the heart rate was between 61 and 99 beats per minute during the entire period of observation (table 11). Combined ventricular (congestive heart) failure occurred in 60.7 per cent of these patients. The mortality was 20.3 per cent. With the normal rate and rhythm and the lower incidence of combined ventricular failure, 23 (58.7 per cent) of the 39 deaths were due to congestive heart failure. However, a hypertensive patient in whom cardiac failure developed and whose heart rate remained regular and did not go above 99 beats per minute had a good chance to recover completely.

Sinus Tachycardia.—The importance of tachycardia as a prognostic sign and as an index of hypertensive heart failure has not been mentioned heretofore. With the cardiac rate between 100 and 150, as it was in 222 (52.6 per cent) of the 422 patients with regular sinus rhythm, the incidence of combined ventricular (congestive heart) failure rose to 80.1 per cent and the mortality to 39.2 per cent. This was a 20 per cent increase, both in the incidence of congestive heart failure and in the mortality over the values for patients with a normal heart rate. The ratio of the causes of death in the two groups remained in proportion.

Simple Bradycardia.—Exclusive of the cases of heart block, 9 men (2.1 per cent) had a persistent heart rate between 50 and 60 beats per minute. In 5 of these (55.5 per cent) congestive heart failure developed, and the mortality was 22.2 per cent. There was little difference as to the degree of failure and the mortality between those who had simple bradycardia and those who had a normal heart rate.

SYMPTOMS

Frequently the first definite indication of cardiac involvement was the appearance of an arrhythmia. In one fourth of the patients who had auricular fibrillation the arrhythmia was the first sign, and because

13. Master, A. M.; Dack, S., and Jaffe, H. L.: Disturbances of Rate and Rhythm in Acute Coronary Artery Thrombosis, Ann. Int. Med. **11**:735. 1937.

of the rapid irregular rate, evidence of myocardial insufficiency appeared within a few days. Although multifocal ventricular extrasystoles, auricular flutter and paroxysmal tachycardia were not as common, it was true also of them. The rapid rate induced such symptoms as palpitation, breathlessness, weakness and occasionally precordial distress or even actual pain. Severe symptoms were generally noted with the sudden onset of rapid fibrillation, auricular flutter or paroxysmal tachycardia. The sudden onset and the appearance of the patient often gave the impression of acute coronary occlusion, but the quick improvement and the adaptation of the undamaged heart to the rapid ventricular rate usually disproved the original diagnosis.

At the other extreme were the effects of a slow ventricular rate, as in complete heart block, which occasionally manifests itself clinically by attacks of the Adams-Stokes syncope, convulsions and coma. This syndrome was an exceedingly rare occurrence during the course of hypertensive heart disease. It was noted only once among 6 cases of complete heart block in my series. One patient had no evidence of congestive heart failure, but died one week after the onset of the heart block, during an attack of the Adams-Stokes syndrome.

MECHANISM OF PRODUCTION OF ARRHYTHMIAS IN HYPERTENSIVE HEART DISEASE

It is difficult to explain the occurrence of arrhythmias in a heart which shows no involvement other than hypertrophy of the muscle fibers and dilatation of the organ itself. Of all the factors which seem necessary to initiate a cardiac arrhythmia, the important one here is impaired nutrition or altered metabolism of the heart muscles. The relation of anoxemia to the arrhythmias is not easy to determine. In evaluating the effects on the heart of acute thrombosis of the coronary arteries, it has been accepted as the mechanism behind the production of the arrhythmias. However, in cases of hypertension in which no evidence can be found in the heart of definite disturbances in the muscle or in the blood supply, this theory is seriously questioned. No doubt there are temporary deficiencies in nutrition of the heart and interference with the metabolic activities in order to bring about such marked disturbances in rate and rhythm.

The relationship between anoxemia and the cardiac irregularities was emphasized by Carter, Andrus and Dieuaide.[14] No marked changes in the coronary arteries are necessary in order to have anoxemia of the heart muscle. In hypertension the great increase in muscle mass, with

14. Carter, E. P.; Andrus, E. C., and Dieuaide, F. R.: A Consideration of the Cardiac Arrhythmias on the Basis of Local Circulatory Changes, Arch. Int. Med. **34**:669 (Nov.) 1924.

the demand for a greater capillary blood supply, is generally met and compensated for by enlargement of the heart. When the rate is normal there is difficulty only after many years. When the rate becomes rapid local anoxemia is more apt to occur and to induce arrhythmia. Anoxemia leads to the local accumulation of lactic acid, which interferes with the development of the excitatory process and its normal propagation. Thus there may be a local area in which diminished conductivity or spontaneous excitation may give rise to an ectopic rhythm. In particular, anoxemia may decrease the refractory period in the auricles, leading to the "circus movements" of auricular fibrillation and flutter.

The relationship of heart failure to arrhythmias, especially auricular fibrillation, has been discussed by Luten.[15] He stated that the tachycardia which occurs in heart failure is a compensatory mechanism and that auricular fibrillation usually is secondary to, and not the cause of, the heart failure. He expressed the belief that in the presence of auricular damage dilatation and stretching of the auricular wall from increased intra-auricular pressure associated with ventricular insufficiency is the predisposing factor in the production of auricular fibrillation. The same explanation could be applied to auricular flutter and auricular tachycardia. Vaquez [16] and Nahum and Hoff [17] also concluded that auricular distention is responsible for the frequent association of auricular fibrillation and heart failure.

Tachycardia often develops in the presence of a hypertrophic heart and usually brings on premature failure.[18] During diastole the left ventricle receives its blood supply, and an increase in heart rate interferes with the oxygenation of the heart muscle fibers. The tachycardia not only goads the weak muscle to more frequent contractions but deprives the harassed myocardium of adequate nourishment. The importance of this mechanism of heart failure in hypertensive heart disease, and not that of ventricular failure plus auricular distention, is substantiated. In over one fourth of patients with hypertensive heart disease the fibrillation preceded and precipitated the congestive heart failure. It was in such patients that the arrhythmia influenced the course of the disease. The fibrillation had no influence on the ultimate course of the disease

15. Luten, D.: The Relationship of Tachycardia to Cardiac Insufficiency, Am. Heart J. **12**:435, 1936. Luten, D., and Jeffreys, E. O.: The Clinical Significance of Auricular Fibrillation, J. A. M. A. **107**:2099 (Dec. 26) 1936.

16. Vaquez, H.: Diseases of the Heart, Philadelphia, W. B. Saunders Company, 1924, p. 603.

17. Nahum, L. H., and Hoff, H. E: Auricular Fibrillation in Hyperthyroid Patients Produced by Acetyl-β-Methylcholine Chloride, with Observations on the Role of the Vagus and Some Exciting Agents in Genesis of Auricular Fibrillation, J. A. M. A. **105**:254 (July 27) 1935.

18. Murphy, F. D.; Woods, R. M., and Grill, J.: Hypertensive Heart Disease, Minnesota Med. **20**:627, 1937.

among those in whom the congestive heart failure was present before the arrhythmia appeared. Also, in those with auricular flutter or with paroxysmal tachycardia the arrhythmia invariably preceded and precipitated the heart failure. Lastly, the fact that the rhythm remains regular in the majority of cases of hypertensive heart failure, even in some of the severest forms, speaks against the theory of auricular distention. Heart failure with dilatation of the auricle probably exerts little or no influence in the initiation of the arrhythmias in hypertensive heart disease. The irregularities are more prone to induce the myocardial insufficiency and precipitate the hypertensive failure.

PROGNOSIS

In general, hypertensive patients with a cardiac arrhythmia had a little better prognosis than those with regular rhythm, mainly because of the infrequency of coronary thrombosis. Exceptions were patients with multifocal extrasystoles and nodal rhythm. From the standpoint of incidence, auricular fibrillation was the most important arrhythmia. It had the lowest mortality, death occurring mainly among those in whom the irregularity preceded and precipitated the congestive heart failure. As to the other arrhythmias noted in table 1, the number of cases was too small to allow any general conclusions.

TREATMENT

Since the arrhythmias in hypertensive heart disease invariably indicate imminent failure of the hypertrophic heart or occur in the presence of insufficiency, and since they are usually permanent, specific treatment with digitalis is almost always necessary. The only other specific drug of value in the therapy is quinidine sulfate, which is especially useful in cases in which auricular fibrillation is the first sign of cardiac involvement. In the absence of congestive heart failure quinidine sulfate is the drug of choice for the treatment of the common arrhythmias.

With the exception of those with the auricular and ventricular types of paroxysmal tachycardia, digitalis is given to all patients with hypertensive heart failure, regardless of whether it is the common combined ventricular type, the less common isolated left ventricular type or the uncommon isolated right ventricular type. Rest in bed is advised and morphine given, depending on the severity of the symptoms associated with the heart failure. Sedatives were used extensively for all the patients in this series, regardless of the fact that many were ambulatory during the treatment for the arrhythmia.

SUMMARY

The study of 243 cases of arrhythmia among 800 cases of hypertensive heart disease, an incidence of 30 per cent, is reported.

The most common arrhythmia was auricular fibrillation; it occurred in 198 (81.5 per cent) of the 243 patients. It had the best prognosis except in cases in which the fibrillation preceded and precipitated congestive heart failure.

Arrhythmia may occur at any time during the course of hypertensive heart disease and often is the first indication of cardiac involvement. It does not tend to show spontaneous remission, to change in character or to become associated with or followed by another type of arrhythmia.

The mortality among patients with arrhythmias was lower than among those with regular sinus rhythm, owing to the comparative absence of coronary thrombosis. Seventy-five per cent of the patients with auricular fibrillation, 66 per cent of those with auricular flutter, paroxysmal tachycardia or complete heart block, 65 per cent of those with extrasystoles and 50 per cent of those with nodal rhythm survived, some of them for a considerable number of years.

The cardiac rate was important as a prognostic sign because the mortality among those with a regular rate above 100 beats per minute was 39.2 per cent, while those with a regular normal rate had a mortality of 20.3 per cent. Of the patients with sinus tachycardia, 80 per cent had combined ventricular (congestive heart) failure, as compared with only 60 per cent of those who had a normal sinus rate and rhythm.

Since the arrhythmia often led to myocardial insufficiency, if this was not evident already, and tended to be permanent, treatment with digitalis or quinidine sulfate was necessary. Digitalis was indicated when the symptoms or signs or both of congestive heart failure were present regardless of the arrhythmia (with the exception of auricular or ventricular types of paroxysmal tachycardia). Quinidine was indicated especially for the treatment of auricular fibrillation or paroxysmal tachycardia in the absence of signs of congestive heart failure.

3507 Lawrence Avenue.

CLINICAL CHARACTERIZATION OF PRIMARY CARCINOMA OF THE BODY AND TAIL OF THE PANCREAS

HYMAN LEVY, M.D.
AND
S. S. LICHTMAN, M.D.
NEW YORK

Carcinoma of the body and tail of the pancreas is by no means a rarity, yet its diagnosis is felt to be difficult because physical findings are commonly absent and the symptom complex is vague in many of the cases.

The clinical characteristics of primary neoplasm of the head of the pancreas have been recognized since Dieulafoy [1] described jaundice due to obstruction of the common bile duct. In 1908 Chauffard [2] differentiated between the cancer involving the head of the pancreas, termed *pancreatico-biliaire,* and that involving the body and tail, designated *pancreatico-solaire.* The latter characterization was based on the supposed localization of the pain in the region of the solar plexus, as a result of invasion by the pancreatic tumor. This type of pain, however, is observed only in isolated instances.

Several observers have described a definite mental pattern of anxiety, nervousness, depression and insomnia in patients suffering from carcinoma of the pancreas.[3] Some of these patients have been labeled as psychoneurotic; yet, despite the absence of objective findings, the pain has been so constant as to arouse suspicion of a definite organic lesion.[4]

Between the years 1926 and 1935, inclusive, the opportunity was afforded us to observe 19 patients with carcinoma of the body and tail of the pancreas. We have analyzed our observations in an endeavor to formulate more satisfactory diagnostic criteria.

From the Medical Division, the Mount Sinai Hospital; service of Dr. George Baehr.

1. Dieulafoy, G.: Manuel de pathologie interne, ed. 15, Paris, Masson & Cie, 1908, vol. 2, p. 1038.

2. Chauffard, M. A.: Le cancer du corps du pancreas, Bull. Acad. de méd., Paris **60**:242, 1908.

3 (*a*) Yaskin, J. C.: Nervous Symptoms as Earliest Manifestations of Carcinoma of the Pancreas, J. A. M. A. **96**:1664 (May 16) 1931. (*b*) Latter, K. A., and Wilbur, D. L.: Psychic and Neurologic Manifestations of Carcinoma of the Pancreas, Proc. Staff Meet., Mayo Clin. **12**:457, 1937.

4. Bourne, G.: Pain as the Only Sign of Pancreatic Carcinoma, Lancet **2**:1326, 1936.

ANALYSIS OF PHYSICAL FINDINGS

One hundred and twenty-two cases of primary malignant neoplasm of the pancreas, in which the diagnosis was confirmed by laparotomy or necropsy, have been studied. From among these, 19 cases in which the neoplasm involved primarily the body and tail of the pancreas have been selected as suitable for study.[4a] The clinical data are summarized in table 1.

TABLE 1.—*Clinical Data*

Case	Sex	Age, Yr.	Duration of Symptoms, Mo.	Presenting Symptom at Onset	Gastrointestinal Symptoms: Anorexia	Gastrointestinal Symptoms: Vomiting	Diabetes, Duration	Loss of Weight: Lb.	Loss of Weight: Mo.
1	F	50	1	Ascites, edema of legs.	+	0	9 mo.	40	18
2	M	47	5	Abdominal pain.....	+	0	.....	40	2
3	M	47	4	Epigastric pain.....	+	0	17 yr.	16	4
4	M	49	6	Epigastric pain.....	+	0	.....	36	5
5	M	69	2	Lumbar pain.....	+	0	.....	21	2
6	F	55	3	Asthenia.....	+	0	8 yr.	15	3
7	M	60	3	Epigastric pain.....	+	0	.....	20	3
8	M	42	1½	Pain in left lower quadrant of abdomen and lumbar pain	+	0	.....	20	2
9	M	65	2	Swelling of left lower extremity	+	0	.....	..	..
10	F	59	3	Abdominal pain.....	+	0	.....	26	24
11	M	52	1½	Lower posterior thoracic pain	+	0	.....	15	2
12	F	56	5	Pain in left lower quadrant	+	0	.....	33	5
13	F	47	37	Anorexia, pain in left thigh	0	0	.....	..	..
14	M	69	½	Pain in left upper quadrant of abdomen	+	+	2 wk.	70	48
15	M	37	5	Umbilical pain.....	+	0	.....	28	4
16	M	24	12	Epigastric pain.....	+	0	.....	90	24
17	M	50	1	Lumbar pain.....	+	0	.....	20	1
18	M	53	5	Abdominal pain.....	+	0	.....	..	..
19	F	53	30	Epigastric pain, vomiting	+	+	.....	50	30

4a. These 19 cases, in which only the body and tail of the pancreas were involved, comprise 15 per cent of the 122 cases of pancreatic carcinoma. This incidence may be compared with the percentages reported by others: 46, by Hick and Mortimer;[5] 32, by Eusterman and Wilbur,[6] and 33, by Riese.[7] The lower incidence in our series probably is a result of a stricter selection of cases, which eliminated, as a rule, those in which the head of the pancreas was also involved. Isolated instances in which the involvement of the head of the pancreas was terminal have been included.

5. Hick, F. K., and Mortimer, H. M.: Carcinoma of the Pancreas, J. Lab. & Clin. Med. **19**:1058, 1934.

6. Eusterman, G. B., and Wilbur, D. L.: Primary Malignant Neoplasm of the Pancreas: Clinical Study of Eighty-Eight Verified Cases Without Jaundice, South. M. J. **26**:875, 1933.

7. Riese, H.: Die Chirurgie des Pankreas, in Kirschner, M., and Nordmann, O.: Die Chirurgie, Berlin, Urban & Schwarzenberg, 1927.

Age and Sex.—There were 12 male and 7 female patients in the series. There was 1 man in the third and 1 in the fourth decade of life; 4 men and 1 woman in the fifth; 4 men and 4 women in the sixth, and 2 men and 2 women in the seventh. Of the 7 patients under 50 years, all but 1 were males.

Duration of Symptoms.—Symptoms were present for from three weeks to approximately a year before hospitalization. Two patients with malignant degeneration of pancreatic cysts had symptoms of longer duration—two and one-half and three years, respectively.

Mode of Onset.—In 15 of the 19 patients the presenting symptom was some type of pain. In the remaining 4 the initial symptoms were, respectively, anorexia, asthenia, ascites and swelling of the lower extremities.

Weight Loss.—For 15 patients loss of weight was accurately recorded, nine of these lost weight over a period of four months or less; the loss ranged between 15 and 40 pounds (7 and 18 Kg.) and averaged 21.5 pounds (9.5 Kg.). The remaining 6 patients lost weight over a period of four to thirty months; the loss ranged between 20 and 50 pounds (9 and 22.5 Kg.) and averaged 34 pounds (15.5 Kg.).

Distribution of Pain.—Of the 18 patients who exhibited pain at some time during their clinical course, 13 had abdominal pain. This pain was diffuse in 3; in 6 it was restricted to the epigastrium, in 2 to the left upper quadrant, in 1 to the left lower quadrant and in 2 to the umbilicus.

Lumbar pain occurred in 4 patients. It was bilateral in 1, on the left side in 2 and on the right side in the fourth. There was radiation of the pain to both inguinal regions in 1 patient and to the outer aspect of the thigh in 2 patients.

In the remaining patient, an unusual distribution of pain was noted, encircling the left lower portion of the chest, from the lower thoracic spine around the left side of the hypochondrium to the xiphoid process.

Gastrointestinal Symptoms.—Marked anorexia occurred in all but a single patient. Vomiting occurred in but 2 patients. Diarrhea did not occur; constipation was noted in several patients.

Cough.—Of 4 patients who exhibited cough as a symptom, in 2 it could be attributed definitely to neoplastic invasion of the lung and mediastinum. In a third patient the cough was conditioned by associated bronchiectasis.

Ascites.—In 6 patients ascites developed. It was hemorrhagic in 4; in 2 it was the result of diffuse peritoneal metastases. In 2 patients it was the result of direct extension of the neoplasm into the portal vein. In 2 of the patients there was swelling of the lower extremities; in the first it resulted from thrombosis of the left common iliac vein, and in the second it was probably secondary to the ascites.

Associated Diabetes Mellitus.—Impaired carbohydrate metabolism was noted in 5 patients. Diabetes mellitus had existed in 2 patients for seventeen and eight years, respectively. In a third patient known diabetes had preceded the onset of the new symptoms by only nine months. In the remaining 2 patients, disturbed carbohydrate metabolism became manifest by hyperglycemia or decreased tolerance as shown by the dextrose tolerance test or both.

Venous Thromboses.—Six patients exhibited venous thromboses resulting mainly from direct neoplastic compression or extension. In 1 patient the portal and splenic veins were involved. In 2, the splenic vein alone; in another, mediastinal metastases had compressed the superior vena cava, with resulting thrombosis of this structure. In the remaining 2 patients the thrombosis occurred in the left common iliac and in the left femoral vein respectively.

Palpable Mass.—In 9 of the 19 patients a definite *epigastric* mass was palpable at the time of admission. In 2 others this finding was equivocal. In the remaining 8 patients palpation did not reveal any masses.

Enlargement of Liver and Spleen.—In 13 patients the liver was enlarged to various degrees, as determined either by exploration or at postmortem examination. In practically every instance the enlargement was directly associated with diffuse hepatic metastases.

The spleen was enlarged in 3 patients. The greatest enlargement was the result of carcinomatous invasion and obliteration of the portal vein. In another patient the splenic vein was obliterated through compression by the tumor. In the third patient, the spleen was only slightly enlarged as a result of metastases within it.

ANALYSIS OF LABORATORY FINDINGS

Hemoglobin Estimations.—The hemoglobin content of the blood was determined in 18 of the 19 cases. In 16 the hemoglobin content was above 70 per cent; in 7 it ranged between 80 and 90 per cent; in 4, between 90 and 100 and in the remaining 5 between 70 and 80.

In the two instances in which the hemoglobin content fell below 70 per cent, it was 67 and 48 per cent, respectively. The latter low level occurred in the youngest member of the group, who had been ill for one year and in whom widespread metastases had been present for many months.

Leukocytosis.—In 11 of 18 cases the leukocyte count was 10,000 or more (10,400 to 28,800), and the percentage of polymorphonuclear cells ranged between 66 and 92. In 2 of the remaining 7 cases the leukocyte count was less than 6,000.

Icterus Index.—In 7 of the 9 instances in which the icterus index was determined it was normal.

Cholesterol Partition.—Cholesterol of the blood was determined in 8 cases, and in 7 the value was normal. In a single instance hypercholesteremia (340 mg. per hundred cubic centimeters) was present (case 11, table 2). In 5 instances the cholesterol ester fraction was determined and was found normal except in 1 instance (case 5), in which the ester fraction decreased to a mere trace.

Blood Amylase.—In 5 cases blood amylase was determined by the method of Elman.[8] In 3 it was at the lower limits of normal. In only 1 instance (case 11) was it increased—to 17.5 and to 15 units.

Blood Sugar.—Estimations of blood sugar were made in 11 instances. In 6 a normal level was found. Hyperglycemia (145 to 395 mg. of sugar per hundred cubic centimeters) was noted in the remaining cases. In 3 instances dextrose tolerance was tested. A sugar tolerance curve of the diabetic type was obtained in 2 cases (10 and 11).

Occult Blood in Stool.—The guaiac test for occult blood in the stool was made in 11 cases. In only 2 did the test prove positive.

Roentgen Findings.—In 9 cases the gastrointestinal tract was studied after a barium sulfate meal. In 3, the findings were negative. Of the remaining 6 cases, in 3 the examination showed gastric and prepyloric defects and in 3 duodenal distortion or defect.

---

8. Elman, R.; Arneson, N., and Graham, E. A.: Value of Blood Amylase Estimations in Diagnosis of Pancreatic Disease, Arch. Surg. **19**:943 (Dec.) 1929.

TABLE 2.—*Laboratory Data*

TABLE 2.—*Laboratory Data*

Case	Hemoglobin, %	Leukocytes, Thousands	Polymorphonuclear Neutrophils, %	Icterus Index	Van den Bergh Reaction	Cholesterol / Cholesterol Esters, Mg. per 100 Cc.	Bilirubinemia, Mg. per 100 Cc.	Blood Amylase, Units	Gastric Acidity	Occult Blood in Stool	Pancreatic Ferments	Blood Sugar, Mg. per 100 Cc.	Roentgen Findings	Special Pathologic Changes
1	80	12.2	86	..	.....	.....	0.7	...	.....	0	.....	330	.....	Stenosis of portal vein
2	72	24.0	88	..	Dir.: neg. Ind. 1/125,000	190	0.8	...	.....	0	.....	...	.....	Hemorrhagic peritoneal fluid
3	85	6.0	56	9	Dir.: neg. Ind. 1/500,000	220/70	0.2	1.8	14/34	0	Trypsin neg. diastase 80	215	Gastrointestinal tract normal	
4	98	7.7	70	..	.....	.....	...	...	40/50	0	.....	...	Incomplete duodenal obstruction	
5	87	7.0	58	7	Dir.: neg. Ind. 1/500,000	205/trace	0.2	1.3	.....	0	.....	120	Gastrointestinal tract: 1. posterior wall lesion? 2. normal	
6	70	13.0	87	..	.....	.....	...	...	.....	0	.....	395	Pleural effusion	Pulmonary embolic thrombosis of splenic vein
7	..	....	..	..	.....	.....	...	...	16/40	—	.....	106	Prepyloric distortion	
8	85	9.0	73	..	Dir.: neg.	.....	0.3	...	36/42	—	.....	104	Gastrointestinal tract normal; barium sulfate enema neg.	Infiltration of stomach, spleen, adrenals, liver and hepatic duct
9	75	15.5	92	..	.....	280	...	...	.....	—	.....	145	.....	Thrombosis of left common iliac vein and vena cava; invasion of left adrenal and left ureter
10	81	10.4	66	25	.....	.....	0.9	...	/44	0	.....	235	Duodenum dilated, antiperistalsis	Compression of portal vein, obliteration of splenic vein, left hydronephrosis
11	82	6.3	76	60 (late)	Dir.: pos. on later admission	340/170	2.5 (late)	17.5 14.9	22/42	—	Trypsin neg. diastase trace	85	Gastrointestinal tract normal; gallbladder faintly visualized	
12	67	5.3	52	7	Dir.: neg.	.....	0.2	...	0/20	0	.....	...	Prepyloric defect	
13	92	14.0	78	7	Dir.: neg.	225/70	0.2	...	.....	—	.....	...	.....	Hemorrhagic peritoneal fluid
14	100	21.5	92	..	.....	.....	...	...	.....	—	.....	350	.....	Hemorrhagic peritoneal fluid, carcinominatous thrombosis of splenic and portal veins
15	98	13.0	79	8	Dir.: neg.	.....	0.3	1.8	64/56	+	.....	...	Gastrointestinal tract: filling defect of duodenum, with retention; gallbladder: failure of visualization	
16	48	5.4	75	..	Dir.: neg.	.....	0.2	...	.....	—	.....	75	Widespread bony metastases	
17	78	28.8	88	12	Dir.: neg.	180/37	0.2	...	.....	—	.....	...	Flat plate of abdomen negative	Peripancreatic abscess, hepatic abscess, subdiaphragmatic abscess
18	82	12.7	76	..	.....	.....	...	...	.....	0	.....	...	Pulmonary metastases	Metastases to upper lobe of right lung. thrombosis sup. vena cava
19	75	15.0	64	9	.....	160	...	6.4 1.0	.....	Trace	.....	85 125	Enlarged mediastinal glands	Thrombosis of left femoral vein, embolus to branch of right pulmonary artery

RÉSUMÉ OF SIGNIFICANT FINDINGS

A review of the more important findings in the analysis of our material indicates that carcinoma of the body and tail of the pancreas occurred in a significant percentage of cases of carcinoma of the pancreas in men under 50 years of age. The outstanding symptoms were pain of various types, rapid loss of weight, marked loss of appetite and a tendency, in some patients, to a disturbance in carbohydrate metabolism similar to diabetes mellitus. In half of the patients a definite abdominal mass was palpable. In the majority of the patients there was hepatic enlargement and in a few splenic enlargement. In over half the patients either ascites or venous thromboses occurred. Anemia was remarkable by its absence. Roentgen examination of the gastrointestinal tract gave material diagnostic aid in the majority of the instances in which it was employed; gastric and duodenal distortion and defects were often demonstrable.

COMMENT

Disease of the body and tail of the pancreas provides a great diagnostic problem. Buried deep in the abdomen and provided with a narrow duct through which a colorless secretion drains into the bowel, the pancreas challenges the scrutiny of the physician.

In about one sixth of the cases neoplastic disease of the pancreas involves the body and tail alone. Because of the frequency of secondary or terminal invasion of the head it is likely that among cases of the disease in the earlier stages the percentage of cases in which the body and tail alone are involved is greater. Victims of the disease under the age of 50 are predominantly males.

Symptoms may be present for as long as one year before medical advice is sought by the patient, and when the malignant change supervenes on a pancreatic cyst the interval may extend to as long as three years.

Appreciable losses of weight (averaging 27 pounds) are characteristic. So constant and striking has this finding been, that when the symptom is observed in the absence of other diseases that regularly produce loss of weight, such as diabetes, hyperthyroidism, tuberculosis, anorexia nervosa, sprue or demonstrable malignant growth, one should suspect and attempt to exclude tumor of the pancreas.

Pain.—Because of the paucity of objective physical and laboratory findings in the disease, pain, which was present in 90 per cent of our patients, is a particularly important symptom. A great variety of types of pain may occur; hence mistaken diagnoses of spondylitis, sciatic syndrome, intercostal neuralgia, renal calculus or diaphragmatic pleurisy may be made. Pain was the presenting symptom in 80 per cent of our

patients and in 44 per cent of the patients studied by Mussey.[9] It was the only symptom in a case reported by Bourne.[4] There are two main components to the abdominal pain, an anterior upper abdominal and a posterior lumbar radiation. Eusterman and Wilbur [6] studied the radiation of pain in 62 patients with malignant tumor of the pancreas and found that in one third of them the pain radiated to the back either directly or around the costal margins. In another one third of the patients the pain did not radiate. In 9 patients the pain radiated to the upper quadrants of the abdomen, to the left in 4 and to the right in 5. A rare but interesting radiation is toward one or the other thigh. Hick and Mortimer [5] reported a case in which the tumor tissue had invaded both ureters, from retroperitoneal metastases, thus producing hematuria and pain radiating to the groins. One patient in our series presented a similar type of radiation of pain, and necropsy revealed that the ureter was invaded by the tumor.

When the pain radiates toward the right side it may simulate that of gallbladder disease. When it is persistently epigastric and radiates through to the back it simulates that of a penetrating lesion of the stomach, either an ulcer or a carcinoma; frequently, however, the pain is unrelated to events of the digestive cycle. It often extends bandlike around the left side as a girdle zone, involving a somatic area innervated by the eighth to eleventh dorsal nerves, and simulates the segmental pain of radiculitis and spondylitis [10] (case 11). Katsch [11] reproduced pain typical of pancreatic disease by instilling 2 to 4 cc. of ether into the duodenum. The weight of the food-filled stomach pressing against the celiac plexus in some cases further increases the irritation of this structure and elicits pain. Similarly, lying supine or leaning backward produces pressure which causes deep-seated epigastric pain extending to the back and radiating as if along the course of a lower intercostal nerve. The initial left-sided pain is probably conditioned by implication of the splenic nerve and its branches; when the entire solar plexus is invaded the pain takes the typical location, median, transverse and supraumbilical.

Latter and Wilbur [3b] recently characterized the pain as more closely resembling that of lesions of the nervous system, such as root pain, than that of visceral disease.

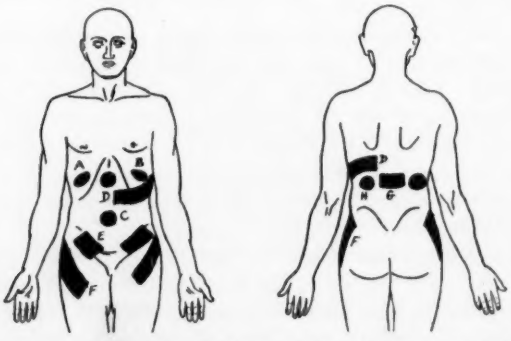
Chauffard referred to pains, simulating "gastric crises," of bulbospinal origin and also a "pseudo-aneurysmal" type. He also pointed out

9. Mussey, R. D.: Pancreatic Carcinoma, M. Clin. North America **3**:681, 1919.

10. Katsch, G.: Krankheiten der Bauchspeicheldrüse, in Lehrbuch der inneren Medizin, ed. 3, Berlin, Julius Springer, 1936, p. 926.

11. Katsch, G., and von Friedrich, L.: Bauchspeichelfluss auf Atherreiz, Klin. Wchnschr. **1**:112, 1922.

a most significant characteristic of many patients with pancreatic malignancy—namely, the classic positions which they assume to obtain relief, sitting up, leaning forward in bed, or walking with the body leaning or bending forward at the hips, or lying curled up on the right side. One patient (case 10) assumed the prone position in order to obtain relief. Lying in bed in the usual recumbent position intensifies the pain. Indeed, occasionally the pain makes its first appearance at night, since lying supine places the nervous structures in front of the vertebral column, especially the solar plexus, under tension. Many carcinomas, such as those of the stomach, liver and lung, which metastasize to the retroperitoneal tissues produce pain in the back as a distressing symptom even in the absence of gross metastases to the spine; yet one does not observe postural relief of pain in these instances.



Areas of pain associated with neoplasm of the body and tail of the pancreas: 1, epigastric or solar. *A, B,* radiation to the upper quadrants of the abdomen. *C,* umbilical. *D,* intercostal; radicular; head zone. *E,* groin; radiation from renal zone. *F,* thigh; radiation from renal zone. *G,* lumbar. *H,* loin.

We recall vividly a patient with pancreatic neoplasm who, suffering from persistent epigastric pain, was driven from his bed by the pain and sought relief by walking the hospital corridor. Partial or complete relief from pain by change of posture is a significant feature of the disease. The paroxsymal nature of the pain and the lack of relation to the digestive cycle characterize it further.

The areas in which pain occurred in our patients are represented in the figure. In 13 patients abdominal pain was localized in the epigastrium, the upper portion of the abdomen or the umbilical region. In 5 patients lumbar or loin pain, with or without radiation toward the inguinal region or thigh, was found. Such radiations are apparently conditioned by tissue invasion toward one or the other kidney; in one case the ureter was invaded, with resulting compression and hydronephrosis on the

affected side. While this type of radiation of pain was not the sole symptom in any of our cases, its occurrence was sufficiently frequent to be worthy of stress. The pancreaticorenal types of pain represent regional pain as well as the referred segmental pain of the kidney and pancreas. The inguinal and the thigh pains represent pains referred along the second lumbar segment.

Analysis of the pancreaticorenal types of pain and lesions in the kidney or ureter (table 3) shows no true correlation. However, in 5 of the 19 patients some form of renal pain was present, at times closely simulating that of renal calculous disease.

Abdominal Mass.—Palpation of the tumor is difficult because of the inaccessibility of the pancreas. Examination with the patient in a tub of warm water may facilitate abdominal relaxation and permit palpation. A tumor was palpable in 45 per cent of our patients and in 69 per cent

TABLE 3.—*Anatomic Findings Associated with the Pancreaticorenal Type of Pain*

Case	Distribution of Pain	Anatomic Changes
10	Bilateral anterior abdominal pain, radiating from nipples to iliac crests	Cancerous invasion of left ureter; left hydronephrosis
5	Bilateral lumbar pain radiating first to left and then to right inguinal region	(Exploratory operation done elsewhere)
8	Pain in left lumbar area and in left lower quadrant of abdomen, radiating to outer left thigh	Metastatic nodules in left kidney
17	Right lumbar pain radiating to right thigh and knee	No intrarenal or ureteral involvement; subdiaphragmatic abscess
13	Pain in left lumbar area and in lateral aspect of left thigh	Malignant degeneration of huge pancreatic cyst

of Eusterman and Wilbur's.[6] The gallbladder is more frequently involved in patients with icterus. In our series an epigastric mass was palpable in 50 per cent of the patients. Enlargement of the liver was present in two thirds of the patients. The spleen was palpable in 3.

A tumor in the body of the pancreas is not fixed until quite late (Eusterman and Wilbur) and therefore may descend several centimeters on deep inspiration.

Gastrointestinal Symptoms.—With a single exception, all of our patients suffered from anorexia, which was also a major complaint in 48 per cent of the patients in the series of Hick and Mortimer.[5] According to Raymond,[12] the appetite may remain good despite marked loss of weight in some patients. Two of our patients had vomiting as a symptom.

Diarrhea was infrequent in patients of this series and of those reported by Eusterman and Wilbur [6] and Hick and Mortimer. It occurs

12. Raymond, L.: Cancer du corps du pancreas, Presse méd. **37**:627, 1929.

more frequently when carcinoma of the head of the pancreas has completely occluded the pancreatic and common bile ducts. Bourne[4] found an increase in the percentage of neutral fat in the stools in a few cases.

Occult blood was found in the stools of 2 of 11 patients. In these 2 patients the neoplasm had invaded the stomach and duodenum. In the absence of such invasion no occult blood was found in the stool. This contrasts with the almost constant presence of occult blood in the stools of patients with gastric carcinoma. In the series of Hick and Mortimer the stomach was involved by direct extension of carcinoma of the tail of the pancreas in 6 patients and the duodenum was invaded in 7; the frequent occurrence of blood in the stools is thus explained. The duodenum was involved, to the extent of producing some degree of obstruction, in 10 patients in Eusterman and Wilbur's series of 88.

Metastases.—Metastases must be distinguished from direct extension of the primary pancreatic tumor. Metastases to the lymph nodes in the upper region of the abdomen and to the liver occur most frequently; lymphatic spread to the mediastinal glands and to the pleura also occurs quite frequently. Carcinomatous lymphangitis of the lung has been recorded. In 4 of our patients neoplastic invasion of the lung and mediastinum occurred; in 1 patient it resulted in thrombosis of the superior vena cava and cough. Hematogenous metastases occur rarely; in these rare cases lymphatic extension also occurs.[4] Hick and Mortimer recorded 1 case of carcinoma of the pancreas with metastasis to the umbilicus. Hemorrhagic ascites developed in 2 patients as a result of diffuse peritoneal metastases.

Carbohydrate Metabolism.—Although hyperglycemia or frank diabetes mellitus occurs only infrequently in this disease, there is a tendency toward decreased carbohydrate tolerance, expressed, when a dextrose tolerance test is given, in a high or delayed dextrose curve. In our own series there were 5 patients with diabetes preexisting to or coexistent with pancreatic tumor. In 1 patient the duration of diabetes was seventeen years; in another, eight years. In a third patient diabetes antedated the other symptoms by nine months, and in a fourth, by two weeks. In a fifth patient there was no preceding history of diabetes, but at the time of admission the blood sugar was found to be 235 mg. per hundred cubic centimeters. Of these 5 patients, in 3 the diabetes was related to the pancreatic disease; the incidence of coexisting diabetes in the series was thus 15 per cent. This is higher than the usual incidence (5 to 8 per cent) encountered in routine hospital practice in the same age group. Dextrose tolerance tests have hitherto been performed infrequently on patients with pancreatic malignancy. It is interesting to note that in 1 patient (case 11) the blood sugar during fasting

was 85 mg., yet the dextrose tolerance test showed a curve with a high plateau, the blood sugar rising to 300 mg. at the second hour and remaining at 280 mg. at the end of the third hour. This finding, together with elevated values for amylase, gave a clue to the underlying disease. Blood sugar during fasting was elevated (145 to 395 mg.) in 5 of 14 patients whose blood sugar was estimated. The blood sugar values of the remaining nondiabetic patients in the group ranged from 65 to 145 mg. In the series of cases reported by Eusterman and Wilbur, glycosuria was infrequent; they encountered 1 case of hypoglycemia (blood sugar 40 mg.). In the group reported by Hick and Mortimer there were 8 cases of diabetes, in 3 of which there was carcinoma of the body of the pancreas.

The disturbance in carbohydrate metabolism in our patients differed in several respects from that found in patients with primary diabetes mellitus. It could not be controlled readily by diet or insulin. Occasionally there was an unexplained spontaneous remission of the glycosuria, unrelated to diet or insulin. The fluctuating dextrose tolerance suggested that variations in circulatory and pancreatic duct pressure, rather than tumor invasion, were probably responsible for the glycosuria.

Central Nervous System.—Yaskin [3a] drew attention to the frequency of neurotic and psychic symptoms in patients with pancreatic malignancy. Recently Latter and Wilbur [3b] again called attention to these same symptoms—anxiety and depression coupled with insomnia and nervousness. These authors stated the belief that the psychic manifestations are somehow directly related to the underlying disease process, and they have called attention to similar manifestations which occur in patients with hyperinsulinism due to adenoma of the islands. We have not paid especial attenton to this problem; such manifestations have not been apparent in our patients. However, a disease process notorious for its repeated diagnostic frustrations lends itself well to a variety of symptoms in the neurotic sphere. As often as not the physician brands the patient with such a condition as neurotic and leaves him to his own resources. Anxiety and depression may naturally follow. Regardless of the mechanism, if such neurotic symptoms do continuously prove to be related to pancreatic malignancy they should be respected and should be entertained in the differential diagnosis of vague complaints referred to the upper part of the abdomen. In the presence of significant loss of weight, which is the rule in pancreatic malignancy, one should hesitate to ascribe too much neurotic significance to such symptoms, if they are present. Usually neurotic persons with conversion gastric symptoms maintain or even increase their weight; when loss in weight does occur it is small, except in cases of anorexia nervosa.

Venous Thrombosis.—A clinical manifestation which merits emphasis is venous thrombosis. Thoenes [13] called attention to this as an early manifestation of pancreatic malignancy in 3 cases which he reported. The thrombosis of the veins of the arm occurred before any other clinical evidence of the disease. Umlauft [14] noted thrombosis of the veins of the thigh in 2 of 26 cases of pancreatic cancer and stated that it was allied with the cachectic state. Decreased coagulation time was noted in another case and thrombopenia in 2 others. Venous thrombosis occurred in 8 of our patients; in 6 it was directly related to pressure of the tumor; in 2 it occurred in the lower extremities probably secondary to pressure on the inferior vena cava and to venous stasis.

Roentgenologic Observations.—Up to quite recently roentgen studies have been of limited value. In malignant diseases involving the head of the pancreas there is widening of the C angle of the duodenal curve.[15] When there has been duodenal invasion, there may be duodenal obstruction. Dickson [16] described loss of the valvulae conniventes when a tumor of the body of the pancreas implicated the transverse duodenum. Rigler [17] found that a tumor of the body and tail tended to displace the stomach upward and forward and the transverse colon downward. When the mass of a pancreatic tumor is large it may exert pressure against the adjacent portion of the stomach, producing a filling defect and simulating the appearance of gastric malignancy. Hershenson [18] recently developed a technic to demonstrate pancreatic tumors more clearly by an indirect method. The patient is placed on a tilted table, the abdomen resting against the table. The table is first placed in a vertical position and then is gradually lowered. No filling defect produced on the body of the stomach by a normal retrogastric structure is noted until the table is tilted nearly to its horizontal position; then a localized impression is produced on the midportion of the stomach. When a retrogastric tumor is present, such as a carcinoma of the body of the pancreas, the filling defect becomes noticeable at a point closer to the vertical plane.

---

13. Thoenes, E.: Multiple Venethrombosen, ein bisher unbekanntes Frühsymptom bei Pankreaskarzinom, München. med. Wchnschr. **79**:1677, 1932.

14. Umlauft, W.: Thrombosen und Pankreaskarzinom, München. med. Wchnschr. **80**:607, 1933.

15. Carty, J. R.: Adenocarcinoma of the Head of the Pancreas, J. A. M. A. **96**:549 (Feb. 14) 1931.

16. Dickson, W. H.: Diagnosis of Obscure Abdominal Lesions by the Roentgen Gastro-Intestinal Examination, Am. J. Roentgenol. **10**:540, 1923.

17. Rigler, L. G.: Diagnosis of Extra-Gastrointestinal Masses, Radiology **21**:229, 1933.

18. Hershenson, M. A.: Carcinoma of the Tail and Body of the Pancreas: A Roentgenologic Technique for Its Demonstration, Am. J. Digest. Dis. & Nutrition **3**:835, 1937.

Still another technic for the indirect demonstration of pancreatic tumors has recently been developed by Engel and Lysholm.[19] On an empty stomach, the patient is given an ordinary effervescent powder with a mouthful of Vichy water. The patient is placed in the prone position, and immediately both lateral and anteroposterior roentgenograms are taken. These must be taken quickly, before the carbon dioxide has escaped from the stomach. Engel and Lysholm found that in 23 of 29 control subjects the retrogastric shadow, representing the tissue structures between the stomach and spine, was about the size of the corresponding vertebral body. Enlargement of the pancreas as by tumor was seen as an increase in the size of this retrogastric shadow. In some cases they could demonstrate local depressions into the inflated stomach, indicating localized tumor formations of smaller size. In stout emphysematous subjects the retrogastric shadow was found to be normally larger, probably as a result of the higher placement of the stomach and of the increase in retroperitoneal fat. Scholz and Pfeiffer [20] describe carcinoma of the tail of the pancreas simulating on roentgenologic examination a malignant change in the greater curvature of the stomach.

Another roentgen sign of possible value is worthy of mention. In a patient in our series a barium sulfate enema revealed considerable spasticity of the cecum and ascending colon. The roentgenologist of the hospital Dr. Marcy Sussman had made this observation in a previous case of pancreatic malignancy, and suggested that it might have diagnostic weight. Stern [21] reported 2 cases of pancreatic malignancy and noted that there was abnormal retention of the barium sulfate, with considerable delay in the hepatic flexure. This was so contrary to the usual finding that he considered it of sufficient value to warrant consideration whenever pancreatic malignancy was suspected. In our group, 2 patients when given a barium sulfate meal showed prepyloric distortion. In each the head of the pancreas was also involved. Faintness or failure of visualization of the gallbladder after the use of dye was seen in 2 patients.

Hematologic Findings.—It is significant that in only 2 instances of neoplasm of the pancreas was there anemia (hemoglobin below 70 per cent)—even though secondary metastases had already occurred in many instances.

The usual absence of secondary anemia in malignancy of the body and tail of the pancreas contrasts sharply with the almost universal

19. Engel, A., and Lysholm, E.: A New Roentgenological Method of Pancreas Examination and Its Practical Results, Acta radiol. **15**:635, 1934.

20. Scholz, T., and Pfeiffer, F.: Roentgenologic Diagnosis of Carcinoma of the Tail of the Pancreas, J. A. M. A. **81**:275 (July 28) 1923.

21. Stern, R.: Ueber die Diagnose des primären Pankreaskrebses, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **45**:71, 1938.

presence of secondary anemia in gastric malignancy at the stage of significant loss of weight.

Leukocytosis was present in approximately 50 per cent of the cases. The greatest leukocytosis was found in those instances in which the carcinoma had already metastasized widely, especially those in which hemorrhagic ascites had developed or broken-down intraperitoneal tissue was present.

We have not studied the erythrocyte sedimentation rate in this disease. The rapid rate which others have stressed as of diagnostic importance may be related to malignancy as such, and may thus be of little value in differential diagnosis.

Special Laboratory Data.—Of the procedures which have been reported as diagnostic aids, reliable estimations of blood amylase are sometimes significant. Elevated values were encountered once in our series (case 11). When there is malignant degeneration of pancreatic cysts subnormal values are more likely to be found. Blood lipase values were not abnormal in the cases of carcinoma of the body of the pancreas as reported by Comfort and Osterberg.[22]

The absence of duodenal ferments is a valuable diagnostic finding, but such absence rarely occurs unless the head of the pancreas is involved. Likewise, steatorrhea usually occurs under that condition.

ILLUSTRATIVE CASES

Our material has demonstrated that malignancy of the body and tail of the pancreas may manifest itself in various forms.[23] Unfortunately we cannot describe a typical form or clinical syndrome. We are presenting cases which will illustrate some of the forms in which the disease may manifest itself, as follows:

1. Silent form. Initial manifestations after metastases have occurred, simulating, for example, disease of the chest. Thoracic pain present as a result of pleural metastases (case 2).

2. Simulation of partial high gastrointestinal obstruction, with duodenal stasis (case 10).

3. Simulation of gastrointestinal disease—gastric carcinoma or peptic ulcer. Gastrointestinal bleeding present (case 15).

4. Malignant degeneration of pancreatic cyst (case 19).

5. Peripheral venous thrombosis (case 9).

---

22. Comfort, M. W., and Osterberg, A. E.: Lipase and Esterase in the Blood Serum, J. Lab. & Clin. Med. **20**:271, 1934.

23. Ransom, H. K.: Carcinoma of the Body and Tail of the Pancreas, Arch. Surg. **30**:584 (April) 1935. Duff, G. L.: The Clinical and Pathological Features of Carcinoma of the Body and Tail of the Pancreas, Bull. Johns Hopkins Hosp. **65**:69, 1939.

6. Intra-abdominal suppuration (case 17).
7. Lumbodorsal pain simulating spondylitis (case 11).
8. Pancreaticorenal form (cf. table 3).

FORM 1 (case 2).—*Silent form-initial manifestations after metastases have occurred, simulating, for example, disease of the chest: thoracic pain present as a result of pleural metastases.*

A male process server, 47 years of age, noted, three years previous to his admission to Mount Sinai Hospital, edema of the legs and feet and some dyspnea. (The details of a prior hospitalization are not known.) His immediate history dated back five months, to a night when he was awakened from sleep by severe pain in the lower right side of the chest. Since that time the pain had been continuous and had become progressively more intense. In the course of two months he had lost 40 pounds (18 Kg.); this he attributed to the anorexia accompanying the pain. He appeared chronically ill.

Physical examination disclosed that the lungs were clear. Fluoroscopic examination revealed no parenchymal lesion but some restriction in the descent of the right leaf of the diaphragm. The upper part of the abdomen was rigid, chiefly in the right upper quadrant, where tenderness was elicited. The lower edge of the liver was felt 3 fingerbreadths below the costal margin. Rectal examination disclosed nothing of importance. The hemoglobin was 72 per cent. The white blood cells numbered 24,000, of which polymorphonuclear cells formed 88 per cent. The stool was negative to the guaiac test for occult blood. The temperature ranged beween 99 and 102 F.

The local signs, together with the restricted movement of the right leaf of the diaphragm, the blood count and the pyrexia, pointed to hepatic or subphrenic abscess, possibly secondary to neoplasm and most likely perforated. No pus was obtained when aspiration of the right subphrenic space was attempted. The general debility of the patient contraindicated surgical intervention. The abdomen became distended and rigid throughout, and the patient died two weeks after admission to the hospital.

Postmortem examination revealed 20 cc. of a hemorrhagic fluid in the peritoneal cavity. The cul-de-sac, which contained most of the hemorrhagic fluid, contained many flat nodules, which were over the peritoneal surface of the rectum. The peritoneal aspect of the diaphragm was covered with numerous flat grayish nodules with hemorrhagic peripheral zones, and the liver also showed many unbilicated grayish nodules. The pleura covering the lower lobe of the right lung was infiltrated by several flat neoplastic nodules. The spleen weighed 110 Gm. The splenic vein was ensheathed in tumor masses. The head and first portion of the body of the pancreas were normal. The remaining portion of the body was transformed into a large tumor, the size of a fist and quite firm, which was firmly adherent to the posterior wall of the stomach, into the lumen of which it bulged. On section it was homogeneous, grayish, with hemorrhagic areas. The regional lymph nodes were infiltrated by the neoplastic tissue, and the left adrenal gland was sourrounded by it.

FORM 2 (case 10).—*Simulation of partial high gastrointestinal obstruction, with duodenal stasis.*

A 59 year old woman was admitted to the hospital in 1930, complaining that for about four years she had suffered from progressively severe belching. Three months before admission she began to have epigastric discomfort and a feeling of distention after meals. She had lost 25 pounds (11 Kg.) in weight. Pain of a

peculiar sort, located on both sides of the abdomen and radiating in parallel fashion from the nipples to the corresponding iliac crests, was present. In addition, the abdomen became rigid. She suffered excruciating pain in the back and was relieved only by lying prone.

On admission she was cachectic and weighed 85 pounds (38.5 Kg.). Because of the peculiar reflex rigidity of the abdomen, it was impossible to palpate any viscera. The liver was percussed a hand's breadth below the costal margin. The hemoglobin was 81 per cent, and the white blood cells numbered 10,400. The Wassermann reaction of the blood was negative. The blood urea nitrogen was 10 mg. per hundred cubic centimeters. The blood sugar was 235 mg. per hundred cubic centimeters; the dextrose tolerance test showed a markedly decreased tolerance (fasting blood sugar, 200 mg.; three hours after administration of dextrose, blood sugar 360 mg. and urine sugar 10 per cent). On routine examination, no sugar was found in the urine, but albumin (3 plus) was present. The icterus index was 25. The bromsulphalein retention was 50 per cent at the end of thirty minutes. The stools contained no occult blood, but frequently large amounts of fat were present.

A diagnosis of metastatic neoplasm of the liver was made. To determine the primary focus, a gastrointestinal series of roentgenograms was made. The stomach was normal, but the whole length of the duodenum was dilated and reverse peristalsis was evident. There was retention of barium sulfate in the stomach and duodenum beyond the six hour period. The incomplete obstruction at the duodenojejunal angle was probably the basis for the long-continued belching after meals.

A diagnosis of carcinoma of the body and tail of the pancreas was suggested because of (1) the presence of chronic duodenal stasis with incomplete obstruction at the duodenojejunal angle; (2) the excess of fat in the stools; (3) the decreased tolerance for sugar; (4) the character of the pain and the relief in the prone position.

Two weeks after admission icterus appeared and persisted up to the time of death, one month later. Necropsy revealed a large scirrhous carcinoma of the body and tail of the pancreas, which had invaded the duodenojejunal angle, causing a circular constriction. The splenic vein was occluded completely. The spleen was moderately enlarged and indurated. The porta hepatis was invaded by tumor tissue and the lymph nodes in this region were enlarged; this had caused compression of the common bile duct, near its origin, and of the portal vein. The liver contained numerous metastases. Infiltration of the wall of the left ureter by tumor tissue had, by narrowing the lumen, produced a typical hydronephrosis of moderate degree, with widening of the calices, the pelvis and the proximal 2 inches (5 cm.) of the ureter. The right ureter was not similarly involved. There was no ascites.

FORM 3 (case 15).—*Simulation of gastrointestinal disease—gastric carcinoma or peptic ulcer, gastrointestinal bleeding present.*

The patient, a man of 37, complained of periumbilical pain, present for five months before admission. The pain occurred usually a few minutes after meals, lasted three to four hours and was relieved by the application of a hot water bag or by the ingestion of milk. Postprandial nausea and eructations were also present. Transient icterus, with temporary enlargement of the liver, had been present nine months before admission.

On physical examination no icterus was noted. There was slight epigastric spasm, more marked on the right, and also tenderness in the right upper quadrant of the abdomen, more marked over a slightly tender mass which extended 2 finger-

breadths below the liver and moved with respiration. Bilateral costovertebral tenderness was elicited. The hemoglobin was 98 per cent; the white blood cells numbered 13,000, of which 79 per cent were polymorphonuclear cells. The icterus index was 8, and the van den Bergh reaction was negative. The Wassermann reaction of the blood was negative. The blood amylase was 1.8 units. Examination of urine gave negative results. Of 9 tests for occult blood in the stools, 5 were positive, at irregular intervals. The Rehfuss test meal showed a maximum free acidity of 40. Gastrointestinal roentgenograms taken after the ingestion of barium sulfate showed several filling defects in the proximal half of the descending portion of the duodenum. There was marked delay in gastric motility; at the end of six hours, there was 75 per cent gastric retention. The middle of the descending portion of the duodenum was drawn to the right and apparently fixed. Roentgenograms made after the ingestion of dye failed to visualize the gallbladder on two occasions. Exploratory operation revealed an inoperable carcinoma of the body and head of the pancreas. It had already invaded the posterior aspect of the duodenum and the wall of the gallbladder.

FORM 4 (case 19).—*Malignant degeneration of a pancreatic cyst.*

A 50 year old housewife was first admitted to the hospital in 1933, complaining of cramplike epigastric pain. Before her first admission to the hospital a large mass with a sharp edge had been noted in the left upper quadrant of the abdomen; it extended 4 cm. below the costal margin. On the following day the mass was smaller and its edge indistinct, and the next day it had disappeared. At the time of admission the abdomen was slightly distended. There was tenderness in the epigastrium and left upper quadrant of the abdomen. However, no masses were felt. The hemoglobin was 88 per cent; the red blood cells numbered 5,350,000; the white blood cells numbered 5,000, of which 56 per cent were polymorphonuclear and 11 per cent eosinophilic. The stool was negative for occult blood. The free acidity of the gastric contents after the administration of histamine was 16 degrees. The Wassermann reaction of the blood was negative. The blood sugar was 110 mg. per hundred cubic centimeters. The blood amylase was 6.4 units. Roentgenograms taken after the ingestion of barium sulfate showed a prepyloric spasm but no evidence of an intrinsic lesion in any part of the gastrointestinal tract. The stomach, however, seemed to be displaced by an extrinsic mass. While the patient was in the hospital a mass again became palpable in the left upper quadrant of the abdomen, just below the costal margin.

During the two years after the patient's discharge, several blood counts revealed persistent eosinophilia, the percentage of eosinophils ranging between 5 and 10. The patient continued to vomit intermittently and complained of a vague but steady ache in the left upper quadrant of the abdomen. Loss of weight was progressive, and at the time of her second admission she weighed 50 pounds (22.5 Kg.) less than on the first admission. In the four weeks preceding her second admission the patient had marked anorexia and fever, with no chills.

Examination on admission revealed a large liver which extended 3 fingerbreadths below the costal margin. In the left upper quadrant of the abdomen was a large mass which extended down to the level of the umbilicus with respiration. Its surface was smooth and its consistency hard. There was tenderness on pressure over this area. There was no evidence of ascites. The pelvic and rectal examinations showed no abnormality. The hemoglobin was now 75 per cent; the red blood cells numbered 4,560,000. The white cells numbered 15,100, of which 64 per cent were polymorphonuclear and 9 per cent eosinophilic. The blood amylase was less than 1 unit. The icterus index was 9. The skin test and complement fixation test for echinococcus were negative.

Roentgenographic examination of the abdomen showed a large mass in the left upper quadrant, the lower portion of which reached the crest of the ilium. Pneumoperitoneum showed the spleen to be of normal size.

Vomiting soon set in and the patient's general condition became too poor to permit surgical exploration. Terminally phlebitis developed in the left leg. Necropsy revealed a large pancreatic cystadenocarcinoma with extensive metastases to the regional lymph nodes and liver. Lipomatosis of the tail of the pancreas, with atrophy of the pancreatic tissue, was apparent. When the pancreatic duct was explored, the probe entered the cyst. This served to explain the intermittent presence of an abdominal mass, suggesting that the cystic mass emptied itself through the duct. Other findings were thrombosis of the left femoral vein, embolism of the right pulmonary artery and pulmonary edema. Bronchopneumonia was also present and was the immediate cause of death.

FORM 5 (case 9).—*Peripheral venous thrombosis.*

A housewife aged 65 entered the hospital and died after three days. Her illness had begun only seven weeks before, when swelling of the entire left lower extremity developed. Aside from some weakness, anorexia and marked constipation, the patient had been fairly well until one week before admission, when mild but persistent cough set in. Dizziness and increasing drowsiness were apparent the day before admission. The presenting symptom, coma, was associated with signs of bilateral involvement of the pyramidal tracts, spasticity being present on the left side and flaccidity on the right. Over the base of the right lung there was a sharply outlined area of dulness with diminished breath sounds. A large irregular liver was readily palpable. There was no icterus. The cerebrospinal fluid was under no increased pressure. It contained 13 white cells per cubic millimeter. Culture of the cerebrospinal fluid showed no bacteria, and the colloidal gold curves were normal. The blood urea nitrogen was 22 mg. per hundred cubic centimeters; sugar, 145 mg.; cholesterol, 280 mg. The urine was normal. The temperature ranged from 100 to 101 F.

Necropsy disclosed a scirrhous adenocarcinoma of the tail of the pancreas with metastases to the liver, lungs and pleura. There was a noncarcinomatous thrombosis of the left common iliac vein and almost all its branches. All the veins about the rectum and uterus were thrombosed. A well formed thrombus was seen projecting into the lumen of the inferior vena cava. The spleen was enlarged because of infarction and occlusion of the splenic vein by the encroaching tumor mass. This mass had also invaded the left adrenal and the left ureter, producing hydronephrosis on the left side. Infarcts of the lungs and kidneys and bronchopneumonia were also present. The brain disclosed no metastases or gross vascular lesions. Microscopically there were extensive areas of cortical softening.

FORM 6 (case 17).—*Intra-abdominal suppuration.*

A 50 year old waiter was admitted to the hospital in 1933. For many years he had had recurrent attacks of diarrhea, with as many as ten bowel movements daily. The stool contained mucus but no blood or pus. A history of long-standing unproductive cough was elicited. About three weeks before admission he began to be troubled with pain in the right lumbar region, which became progressively more severe and which occasionally radiated down the right thigh to the knee. No urinary symptoms were associated with the pain. One week before admission there was soreness just below the ribs, and at this time the pain began to radiate upward into the chest on the right side and was aggravated by respiration and cough. There were progressive anorexia and a low grade fever. The patient lost 20 pounds (9 Kg.) in weight. Six days before admission he had a severe

attack of pain in the right side of the abdomen, radiating to the spine and across to the left side of the abdomen. On admission the temperature was 106 F. There was mild generalized abdominal distention. The liver was palpable 4 fingerbreadths below the costal margin. The hemoglobin was 78 per cent; the white blood cells numbered 28,800, of which 88 per cent were polymorphonuclear forms. The blood urea nitrogen was 28 mg. per hundred cubic centimeters, the blood cholesterol 180 mg. and the cholesterol esters 37 mg. The icterus index was 12; the van den Bergh direct reaction was negative, and the indirect reaction was 1: 500,000, with 0.2 mg. of bilirubin. The Wassermann reaction of the blood was negative. The urine revealed no tyrosine. Roentgenograms showed the left kidney to be normal; there was marked ptosis of the right kidney, the lower pole being well below the iliac crest. There was marked enlargement of the spleen.

During the patient's stay in the hospital there was intermittent fever, the temperature varying between 100 and 103 F., with occasional rises to 104 or 105 F. Abdominal distention was persistent. There were occasional pain in the right upper quadrant of the abdomen and some tenderness over the enlarged liver. There were periods during which the patient's general condition greatly improved. Shortly afterward, however, the temperature would rise, the abdomen would again become more distended, and the appetite would diminish. Edema of the sacrum and extremities, which was only moderately relieved by mercurial diuretics, persisted in varying degrees until death. Cultures of blood taken just before chills were experienced were reported negative.

The patient died two months after admission. Necropsy disclosed an adenocarcinoma of the body of the pancreas with metastases to the adjacent lymph nodes and liver; a localized purulent peritonitis with peripancreatic abscess perforating into the stomach; hepatic abscess with perforation into the peritoneal cavity, and a loculated right subdiaphragmatic abscess. Bronchostenosis was present in the lobes of the left lung, but it was not due to carcinomatous metastases.

FORM 7 (case 11).—*Lumbodorsal pain simulating spondylitis.*

A 52 year old counterman had a history of long-standing heartburn, constipation and flatulence. He entered the hospital in 1933 after six weeks of severe sharp constant pain in the region of the thoracic spine, which had soon encircled the left flank and hypochondrium, reaching the xiphoid cartilage. The pain also extended up into the left axilla. There had been anorexia and a loss of 15 pounds (7 Kg.) in weight.

Physical examination revealed a well developed man, somewhat plethoric. The blood pressure was 210 systolic and 122 diastolic. The hemoglobin was 82 per cent; the white blood cells numbered 6,200, of which the polymorphonuclear forms numbered 76 per cent. The cinchophen oxidation test showed evidence of marked disturbance in the function of the liver. The Rehfuss test meal showed a total acidity of 42 and a free acidity of 22. The Wassermann reaction of the blood was negative. Roentgen examination of the spine showed moderate arthritic changes consistent with the patient's age. Roentgenograms at first failed to show the gallbladder, and subsequent visualization of this organ was faint; the gastrointestinal tract appeared to be normal; the chest showed no parenchymal lesion.

The blood amylase level was 175 units. The Janney dextrose tolerance test showed diminished tolerance for sugar on two occasions; on one of these the fasting level was 85 mg. per hundred cubic centimeters; at the end of one and a half hours it was 235 mg.; at the end of three hours it was 300 mg., and at the end of five hours it was 280 mg. On two occasions examination of the duodenal

contents obtained by drainage showed no trypsin. The blood cholesterol was 340 mg., and the cholesterol esters, 170 mg. Because of the amylase level and the dextrose tolerance curve the patient was thought to be suffering from low grade pancreatitis, and cholecystectomy was advised; this the patient refused.

He was readmitted to the hospital two months later with a recurrence of his original pain. An exploratory operation was done, and the pancreas was found to be the seat of a hard tumor, evidently a carcinoma. The liver was normal in consistency but shrunken. The gallbladder was moderately enlarged and contained 3 ounces (88.5 cc.) of thick, concentrated bile. The bile ducts appeared dilated. Cholecystogastrostomy was done. The patient left the hospital, and follow-up records indicated that he died a month after discharge.

SUMMARY

Nineteen cases of primary carcinoma of the body and tail of the pancreas, in which the diagnosis was confirmed by laparotomy or by necropsy, have been observed during a period of ten years.

The symptom complexes that have been encountered are presented. They are explained on the basis of actual neoplastic invasion, local and distant metastases or mechanical pressure.

As a result of our analysis the following clinical signs and symptoms assume diagnostic significance:

1. Rapid loss of weight unaccounted for by diabetes, hyperthyroidism, tuberculosis, anorexia nervosa, sprue or demonstrable malignant tumor.
2. Anorexia.
3. Noncolicky pain in the abdomen—either diffuse or in the upper portion—radiating to the lumbar region, unrelated to the digestive cycle, unrelieved by food, often nocturnal and relieved by change in posture.
4. Absence of anemia.
5. Absence of occult blood in the stool (unless the tumor has invaded the duodenum or stomach).
6. Disturbed carbohydrate tolerance manifested by glycosuria, hyperglycemia or a dextrose tolerance curve of the diabetic type.
7. Atypical roentgen findings in the duodenum or stomach.
8. Elevation of the blood amylase.
9. Hemorrhagic ascites.
10. Peripheral venous thrombosis.

The absence of secondary anemia and of occult blood in the stool and the presence of significant loss of weight sharply differentiate malignant growth of the body and tail of the pancreas from gastric carcinoma, in which significant loss of weight is invariably coupled with secondary anemia and occult blood in the stool.

UREA REABSORPTION AND RELATION BETWEEN CREATININE AND UREA CLEARANCE IN RENAL DISEASE

AARON ARKIN, M.D., PH.D.

Associate Professor of Medicine, Rush Medical College, University of Chicago, and Chairman of the Department of Medicine, Cook County Graduate School of Medicine

AND

HANS POPPER, M.D.*

CHICAGO

Richards [1] has proved by examinations of the glomerular urine of the frog that urea is filtered through the glomerular loops.

The reabsorption of urea in the tubules was demonstrated by investigations based on the theory of Cushny and of Rehberg.[2] Such substances as creatinine are filtered through the glomeruli but are not secreted or reabsorbed in the tubules. With this in mind, one is able to observe the pathway of other substances in the kidney.

The exogenous creatinine clearance method used by Rehberg for the determination of the filtration rate gives reliable results in the dog but not in man (Smith,[3] Shannon [4]). In human subjects administration of creatinine causes an increase in the clearance as a result of secretion. Therefore, the inulin clearance method was employed in the calculation of the filtration rate (Shannon and Smith,[5] Richards and his associates [6]). The endogenous creatinine clearance test probably does not involve this error and gives a more reliable measure of glomerular filtration (Popper and Mandel,[7] Miller and Winkler [8]), as the values are

---

* Research Fellow, Cook County Graduate School of Medicine.

From the Cook County Graduate School of Medicine and the Cook County Hospital, Medical Service of Dr. Aaron Arkin.

1. Richards, A. N.: Proc. Roy. Soc., London, s.B **126**:398, 1938.
2. Rehberg, P. B.: Biochem. J. **20**:447, 1926.
3. Smith, H. W.: The Physiology of the Kidney, New York, Oxford University Press, 1937.
4. Shannon, J. A.: J. Clin. Investigation **14**:403, 1935.
5. Shannon, J. A., and Smith, H. W.: J. Clin. Investigation **14**:393, 1935.
6. Richards, A. N.; Westfall, B. B., and Pott, P. A.: Proc. Soc. Exper. Biol. & Med. **32**:73, 1934.
7. Popper, H., and Mandel, E.: Ergebn. d. inn. Med. u. Kinderh. **53**:685, 1937.
8. Miller, B. F., and Winkler, A. W.: J. Clin. Investigation **17**:31, 1938.

in close accord with those for the inulin clearance (Steinitz and Türkand [9]).

From the theoretic viewpoint for measurement of the filtration rate the inulin clearance test is superior to the endogenous creatinine clearance test. However, the inulin clearance test involves considerable technical difficulty and is not as readily adaptable to the study of a large amount of clinical material as is the test for creatinine clearance, which can be used for routine work.[10]

A comparison of the urine-plasma ratio of urea with that of creatinine or inulin has been made by many authors. Some [11] compared the clearance of exogenous creatinine with that of urea in man; others made similar studies in dogs,[12] rabbits,[13] sheep [14] and chickens.[15] Winkler and Parra [16] and Chasis and Smith [17] used the inulin clearance for comparison, and Ferro-Luzzi [18] published data concerning the endogenous creatinine clearance.

All these examinations showed the urea clearance to be somewhat lower than the creatinine clearance or the glomerular filtration rate, usually 30 to 70 per cent of the latter. This ratio may vary considerably and may rise to 100 per cent, even in normal persons or animals, especially when there is marked diuresis. The maximal urea clearance test of Van Slyke, with a flow of urine of over 2 cc. per minute, demon-

9. Steinitz, K., and Türkand, H.: Tib fak. mec., Istanbul Univ. **2**:1005, 1939.

10. Popper, H.: Klin. Wchnschr. **16**:1454, 1937.

11. (*a*) Covian, C. G., and Rehberg, P. B.: Skandinav. Arch. f. Physiol. **75**: 21, 1936. (*b*) Keith, N. M.; Power, M. H., and Petersen, R. D.: Am. J. Physiol. **108**:221, 1934. (*c*) Bings, J., and Bjering, T.: Acta med. Skandinav. **93**:318, 1937. (*d*) Hayman, J. M., Jr.; Halsted, J. A., and Seyler, L. E.: J. Clin. Investigation **12**:861, 1933. (*e*) Cope, C. L.: Quart. J. Med. **24**:567, 1931. (*f*) Ellis, L. B., and Weiss, S.: Am. J. M. Sc. **186**:242, 1933; Renal Function in Arterial Hypertension, J. A. M. A. **100**:875 (March 25) 1933. (*g*) White, H. L., and Heinbecker, P.: Am. J. Physiol. **123**:566, 1938. (*h*) McCance, R. A., and Widdowson, E. M.: J. Physiol. **91**:222, 1937. (*i*) Rehberg.[2] (*j*) Popper and Mandel.[7]

12. (*a*) Jolliffe, N., and Smith, H. W.: Am. J. Physiol. **99**:101, 1931. (*b*) Shannon, J. A.: ibid. **117**:206, 1936; **123**:182, 1938. (*c*) Kay, W. W., and Sheehan, H. L.: J. Physiol. **79**:359, 1933. (*d*) Van Slyke, D. D.; Hiller, A., and Miller, B. F.: Am. J. Physiol. **113**:611, 1935. (*e*) Hayman, J. M., Jr.; Shumway, N. P.; Dumke, P., and Miller, M.: J. Clin. Investigation **18**:195, 1939. (*f*) Alving, A. S., and Gordon, W.: J. Biol. Chem. **120**:103, 1937.

13. Kaplan, B. I., and Smith, H. W.: Am. J. Physiol. **113**:354, 1935.

14. Shannon, J. A.: Proc. Soc. Exper. Biol. & Med. **37**:379, 1937.

15. Pitts, R. F., and Korr, J. M.: J. Cell. & Comp. Physiol. **11**:117, 1938. Shannon, J. A.: ibid. **11**:123, 1938.

16. Winkler, A. W., and Parra, J. P.: J. Clin. Investigation **16**:869, 1937.

17. Chasis, H., and Smith, H. W.: J. Clin. Investigation **17**:347, 1938.

18. Ferro-Luzzi, G.: Ztschr. f. d. ges. exper. Med. **94**:708, 1934.

strates the same fact, as then the urea clearance is independent of the flow of urine and corresponds roughly with the filtration rate.

According to Rehberg, the variations in reabsorption of urea depend on physical forces within the tubular system. It was previously assumed [7] that the tubular epithelium forms a barrier which regulates the composition of the reabsorbed fluid streaming to the reabsorbing capillaries. The selective permeability of the tubular epithelium undergoes constant changes according to the general needs of the organism. It prevents the back flow of part of the filtered urea, thus concentrating it in the urine. Damage of the tubular cells may impair the function of the barrier and increase the back flow, causing reabsorption uremia (Ferro-Luzzi [18]). These findings correspond with the results of animal experiments performed by Yamaguchi,[19] which revealed the pathologic reabsorption of congo red, creatinine and albumin by damaged tubules. This conception being correct, the reabsorption of urea should increase in the damaged kidney. In contrast, it was assumed [20] that decreased filtration is compensated for by decreased reabsorption of urea in order to increase the urinary output and to prevent retention. This assumption is in accordance with the results of Smith and Shannon.

In order to estimate the amount of reabsorption of urea in a damaged kidney we compared the clearance of urea and that of creatinine in normal and in pathologic conditions. As the method of Popper, Mandel and Mayer [21] permits an exact determination of creatinine at normal blood levels, oral administration could be omitted.

METHOD

Fasting patients were catheterized, and the urine was discarded. They remained in bed, and two to three hours later the bladder was catheterized again and the sample of urine examined. In men a permanent catheter was usually inserted, and in a few cases voluntary emptying of the bladder was permitted. Blood was drawn into a tube containing oxalate. Sometimes two test periods were combined in one day. When creatinine is not administered the amount in the blood does not change, and one determination is sufficient.

The creatinine content of urine and of blood plasma was determined by the absolute colorimetric method,[21] and the urea content, with urease and microdistillation according to the method of Rappaport and Gutmann.[22] The normal creatinine content of the blood varies between 0.6 and 1 mg. per hundred cubic centimeters. Even a slight increase over 1 mg. indicates glomerular insufficiency.[23]

19. Yamaguchi, T.: Tohoku J. Exper. Med. **18**:392, 1931. Shoji, T., and Takeda, K.: ibid. **26**:592, 1935.

20. Popper, H., and Brod, J.: Ztschr. f. klin. Med. **134**:196, 1938.

21. Popper, H.; Mandel, E., and Mayer, H.: Biochem. Ztschr. **291**:354, 1937.

22. Rappaport, F., and Gutmann, M.: Klin. Wchnschr. **14**:1325, 1935.

23. Popper, H.; Mandel, E., and Mayer, H.: Ztschr. f. klin. Med. **133**:56, 1937.

Glomerular filtrate and resorbate were calculated according to the formula of Rehberg.[2] The concentration index (a measure of the concentration of the urine) equals the urine-plasma ratio of creatinine. Excretion of urea was indicated as the excretion percentage, the amount of urea appearing in the urine in per cent proportion to the urea filtered in the glomeruli. It corresponds with the urea-creatinine clearance ratio:

$$E_U = \frac{\frac{\text{urine urea}}{\text{plasma urea}}}{\frac{\text{urine creatinine}}{\text{plasma creatinine}}} \times 100$$

RESULTS

The material includes 191 determinations in 92 cases. Many patients were examined several times on different days in the course of the disease. Table 1 shows the types of cases used. Convalescent patients or those without any pathologic conditions of the kidneys were used as controls. Listed as cases of extrarenal glomerular insufficiency are those in which there was an increase in the creatinine level due to changes in the general circulation without any specific pathologic conditions of the kidneys, such as are found in heart failure, infections and hypochloremia. In the group of cases of hypertension the different types of vascular disease of the kidneys are combined: essential hypertension and benign and malignant nephrosclerosis. In the group of cases of acute nephritis an instance of extraglomerular nephritis is included in which the course was progressive and death resulted from

TABLE 1.—*Excretion Percentage of Urea in Diseases of the Kidneys*

Condition	Number of Cases	Number of Examinations	Excretion Percentage of Urea		
			Maximum	Minimum	Average
Normal	42	76	69.2	6.8	26.4
Acute nephritis	7	12	148	35.4	44.6
Chronic nephritis	8	17	92.5	15.8	49.1
Hypertension	15	39	101	3.0	35.5
Nephrosis	4	13	54.7	24.8	35.1
Pyelonephritis	6	26	176	34.8	67.3
Extrarenal insufficiency	6	8	90	13.7	41.2

uremia within a few days. Under chronic nephritis the severe and the mild forms are combined. The group of cases of pyelonephritis comprises those of contracted kidney due to chronic pyelonephritis, in which the condition is often difficult to differentiate from chronic nephritis. In the cases of a more severe form the diagnosis was often confirmed by autopsy.

Table 1 shows that the excretion percentage of urea in normal persons varies between 6.8 and 69.2, with an average of 26.4 for 76 examinations in 42 cases. In all cases in which there were pathologic conditions the average was higher. In nephrosis the increase is not significant; it is higher in hypertension and in acute nephritis. The difference is marked in the diseases with contraction of the kidney,

such as chronic nephritis or pyelonephritic contracted kidney. The extrarenal glomerular insufficiency shows a slight increase as compared with the normal.

As important as the average increase is the elevation of the excretion percentage over 100 in some conditions. This indicates that the urea clearance is higher than the creatinine clearance. This elevation is far in excess of any error of the method. Repetition of the E_U on the same day shows it to be constant. In examinations with intervals of several days a definite variation occurs (table 2).

TABLE 2.—*Variations in Excretion Percentage of Urea on Different Days*

Patient	Date	Urinary Output, Cc. per Min.	Urine Creatinine, Mg. per 100 Cc.	Plasma Creatinine, Mg. per 100 Cc.	Concentration Index	Creatinine Clearance, Cc. per Min.	Urea Nitrogen in Urine, Mg. per 100 Cc.	Urea Nitrogen in Plasma, Mg. per 100 Cc.	Excretion Percentage of Urea
J	12/16	0.38	308	3.36	91.6	34.5	1,537	18.6	90
	12/18	0.57	190	1.68	113	64.4	1,212	34.1	31.3
		0.56	200	1.68	119	67.1	1,258	34.1	30.8
	12/20	0.70	144	0.97	148.6	118	1,351	32.8	27.8
	12/23	0.38	228	2.16	105.3	40.6	699	25.1	27.5
	1/ 4	1.14	83	1.06	78.3	89.4	513	13.9	47
	1/ 8	0.61	186	0.93	200	121.6	851	12.7	33.6
H	12/ 9	0.83	93	2.40	38.7	32.02	373	32.6	29.5
	12/10	0.77	83	2.29	36.2	27.98	453	27.3	45.9
	12/14	0.58	133	2.59	45.01	26.5	536	28.0	42.5
	12/23	0.77	164	5.72	28.3	21.8	792	72.7	38.6
	1/ 3	1.25	59.1	4.04	14.4	18.08	380	30.3	87
	1/ 5	0.39	162	4.44	36.6	14.06	559	41.9	36.4
	1/ 8	0.66	117	3.96	29.6	19.7	331	48.9	23
		0.66	115	3.96	29.1	19.3	331	48.9	23.2
	1/13	3	68	3.36	22.9	59.8	234	25.6	45.8
		0.91	78	3.36	22.9	21.0	279	25.6	47.5

A plot of the E_U and the urinary output shows a slight parallelism between increase of urine flow and E_U. However, only in persons with normal kidneys is a low urinary output combined with a low E_U, whereas in persons with pathologic conditions it may correspond with a high E_U.

Closer uniformity in the plot is obtained by comparing the E_U with the concentration index, as already done by Shannon [12b] and Chasis and Smith.[17] Figure 1 shows a high concentration index typically combined with a low E_U. An index of over 250 never corresponds with an E_U over 25, while with an index below 60 the E_U is never below 20 and may go as high as 100 or more. The characteristic line of Shannon and Smith, with an angle around the index of 20, is to be seen despite the extensive scattering due to the variety of pathologic conditions. Extrarenal glomerular insufficiency, nephrosis, acute nephritis and benign nephrosclerosis reveal rather normal conditions, in contrast to those in cases of severe renal damage, such as chronic nephritis, pyelonephritic contracted kidney, malignant nephrosclerosis and acute extraglomerular nephritis (1 case).

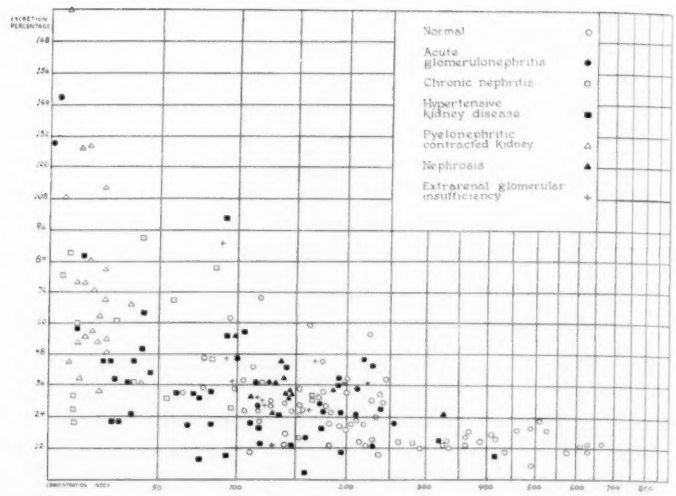


Fig. 1.—Logarithmic plot of excretion percentage of urea and concentration index in various diseases of the kidney.

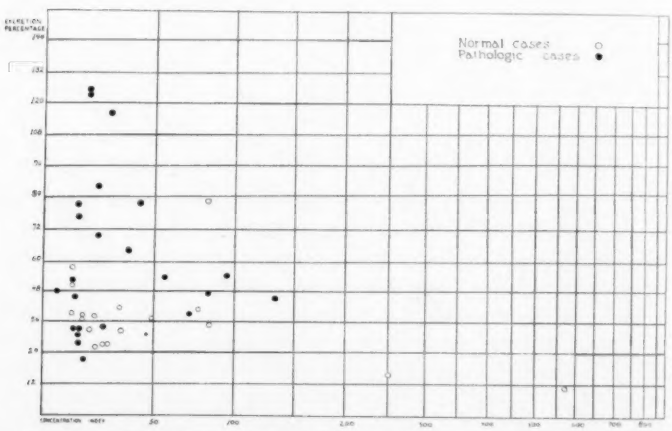


Fig. 2.—Logarithmic plot of excretion percentage of urea and concentration index in 7 patients with normal or slightly damaged kidneys. Each person received 1,500 cc. of fluid and excreted most of this amount within four hours.

Figure 1 confirms Smith and Shannon's finding that there is a direct connection between diminution of the concentration of the urine and increase of the E_V. We obtained a lower index in normal persons by forcing diuresis by the administration of 1,500 cc. of fluid; the same was done in some cases of slight renal involvement. Figure 2 reveals the results of 8 examinations in 7 cases.

In accordance with Smith and Shannon, a falling index leads to an increase of the E_U and thus to an approximation of the urea and the creatinine clearance. However, the decrease in the concentration of the urine may not be the only decisive factor for a low E_U, since in patients with pathologic conditions the E_U is much higher with the same index than in normal persons, as seen by a comparison of figures 1 and 2. This suggests a second factor independent of the low concentration: the presence of a disease of the kidneys.

The plasma creatinine is a measure of renal function, as its increase indicates the degree of impairment in glomerular circulation and filtration. Figure 3 shows a definite connection between the E_U and the creatinine level. With normal or slightly damaged renal function the E_U is low in fasting patients. With the creatinine content below 1 mg. per hundred cubic centimeters the E_U never exceeds 62. With slightly increased creatinine, up to 2 mg., the E_U shows a slight tendency to rise. However, in patients with acute nephritis, nephrosis and extrarenal glomerular insufficiency and in some of the hypertensive patients the values are within normal range. With further increase in creatinine the tendency for the E_U to rise is more definite but not uniform. Next to the highest E_U, together with the highest creatinine level, was found in the patient with extraglomerular acute nephritis who was twice examined. The rise does not take place in all cases in which there is a high creatinine content; however, we never observed an E_U below 20 if the creatinine level was over 2 mg.

As the glomerular filtration rate is related to the plasma creatinine level, there is an increase in the E_U with a decrease in creatinine clearance. In nephrosis the E_U is normal despite the decreased filtration rate.

As decreased reabsorption in fasting persons is a sign of severe disease of the kidneys, it is usually combined with an increasing E_U. Among the patients with diminished reabsorption during fasting those with pyelonephritis show the highest E_U. Thus there is a tendency for the E_U to be low when the filtration and reabsorption rates are reduced.

COMMENT

The examinations show, in accordance with the reports in the literature, the variations in the excreted urea as compared with the filtered urea, and thus the variations in reabsorption of urea. Two factors may influence the reabsorption of urea. The first factor is the amount of diuresis, which is in relation to the degree of concentration of the urine. According to Smith and Shannon, this is explained by physical forces, such as speed of the flow of urine in the tubules. The second factor

24. Footnote deleted.

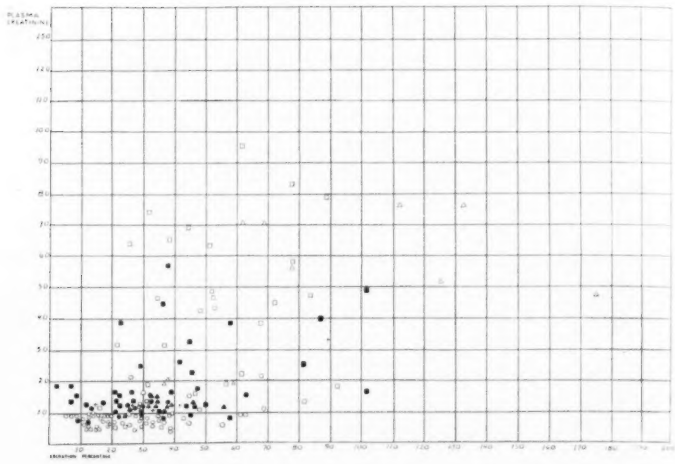


Fig. 3.—Plot of the excretion percentage of urea against the plasma creatinine (milligram per thousand cubic centimeters) in normal persons and in those with pathologic conditions.

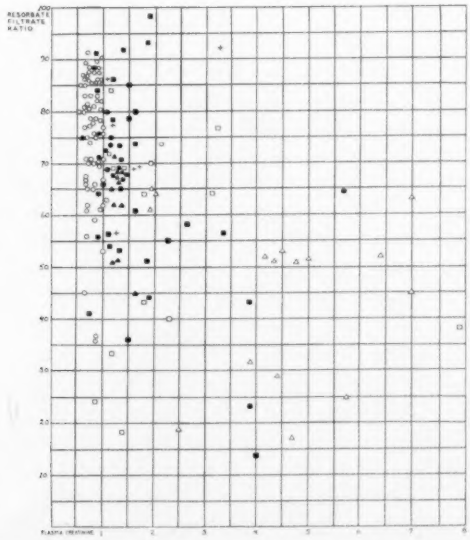


Fig. 4.—Plot of the resorbate-filtrate ratio of urea against the plasma creatinine in normal persons and in those with pathologic conditions.

is the presence of severe damage to the kidney. Patients with glomerular damage of slighter degree and moderately increased plasma creatinine show nearly normal urea reabsorption, as in extrarenal glomerular insufficiency, benign nephrosclerosis, acute nephritis or nephrosis, which now is considered to be a primary glomerular condition.[25] In the uremic kidney diseases, with decreased flow of blood and fluid through the organ (dehydration of the kidney tissue), the urea reabsorption is much diminished, as in chronic nephritis, malignant hypertension, acute extraglomerular nephritis and pyelonephritic contracted kidney. The simplest explanation for the decreased urea reabsorption in these cases is the decreased reabsorption of water.

In a prior study one of us tried to calculate the content of urea in the reabsorbate. The calculation is not logical, since it is now believed that the reabsorbed fluid does not have a uniform urea content. Urea and water are not reabsorbed equally in the same place (Keller,[26] Smith and Shannon). However, in order to answer the question whether the decrease in urea reabsorption depends only on the decreased back flow of water, the comparison of the urea content of a hypothetic uniform reabsorbate with that of the filtrate or plasma is significant. The calculation is made according to the following formulas,[2] which point out the resorbate-filtrate ratio.

$$\text{Reabsorbate urea} = 100\,\frac{(\text{plasma urea} \times \text{filtration rate}) - (\text{urine urea} \times \text{urinary output})}{\text{reabsorption rate}}$$

$$\text{Reabsorbate-filtrate ratio } (U_R) = \frac{\text{reabsorbate urea}}{\text{plasma urea}} \times 100$$

U_R is a measure of the antiosmotic force effective in the tubules, which force is stronger when the ratio is lower. A plot of the U_R against the plasma creatinine as a measure of the involvement of the kidney reveals a definite decrease in the U_R in cases of pathologic kidneys. In normal persons the average is about 72. A decrease corresponds with the degree of kidney disease and is moderate with slightly impaired glomerular function.

The relatively low urea content of the hypothetic reabsorbate as compared with that of the filtrate in kidney disease indicates strong antiosmotic forces effective at the epithelial barrier against the attempted backward diffusion of urea. Thus, the low urea reabsorption is explained not only by a decreased back flow of fluid but by an actual counteraction. Increased reabsorption can therefore be excluded, and we join Smith in not recognizing the association of reabsorption uremia with diseases of the kidneys.

---

25. Randerath, E.: Ergebn. d. allg. Path. u. path. Anat. **32**:91, 1937. Bell, E. T.: Am. J. Path. **14**:691, 1938.

26. Keller, R.: Der elektrische Faktor der Nierenarbeit, Mährisch-Ostrau, Verlag Julius Kittls Nachfolger, 1933.

Important are the few examples in which the E_U is over 100. If more urea is excreted than filtered, secretion of urea may be assumed. It could be argued that in the damaged kidney a reabsorption of creatinine exceeding that of urea takes place, which would explain the relatively low creatinine clearance. This is not probable from a physical point of view, as the diffusion gradient of urea is higher than that of creatinine.[27] Recent studies of McCance and Widdowson [28] have shown a pathologic back flow of creatinine in cases of diabetic coma. This is not likely in diseases of the kidney. An approximation of urea clearance to creatinine clearance, or even an excess of urea clearance, is found in several cases of severe kidney damage recorded in the tables of Hayman, Halsted and Seyler[11d] and also in those of Ellis and Weiss.[11f] Both groups of investigators administered creatinine, thus raising the creatinine clearance above the filtration rate, and recorded the standard urea clearance, which was lower than the original urea clearance. Despite that, the urine plasma ratio of urea was in some cases higher than that of creatinine. The possibility of urea secretion in man can therefore be assumed. This fact was also proved in amphibians by Marshall [30] and by Walker and Hudson.[31] We have found that a rise of the urea clearance over the creatinine clearance occurs in rabbits after injection of urine or certain poisons up the ureter with high pressure. The same occurs after selective destruction of the renal pyramid by vinylamine poisoning.

What role may urea secretion play in diseases of the human kidney? With regard to urea reabsorption, we have considered that antiosmotic forces are stronger than normal in cases in which there is severe damage to the kidneys.

If in a pathologic condition a function is increased, a compensatory mechanism must be assumed. This assumption agrees with our previous view that the decreased reabsorption with impaired filtration is an attempt to reduce urea retention. Even in the presence of severe damage to the kidney the epithelium of the still functioning nephrons shows an increased function of the barrier. Disturbed power of concentration of the kidney may be due not to impaired tubular function

27. Bunim, J. J.; Smith, W. W., and Smith, H. W.: J. Biol. Chem. **118**:667, 1937.

28. McCance, R. A., and Widdowson, E. M.: J. Physiol. **95**:36, 1939.

29. Footnote deleted.

30. Marshall, E. K.: J. Cell. & Comp. Physiol. **2**:349, 1932.

31. Walker, A. M., and Hudson, C. L.: Am. J. Physiol. **118**:153, 1937.

32. Footnote deleted.

but to the diminution in reabsorption of water, which is explained by the distribution of the reabsorbing medullary vessels [33] and the dehydration of the kidney tissue.

SUMMARY

The clearance of urea and that of endogenous creatinine were compared in 87 cases of normal and of pathologic conditions in order to estimate the reabsorption of urea.

Urea reabsorption is constant during the same day, but not on different days. It is slightly diminished during fasting in moderate glomerular disorders, such as acute glomerulonephritis, benign hypertension, nephrosis and extrarenal glomerular insufficiency. It is markedly diminished in many cases of severe damage to the kidneys, as in chronic nephritis, malignant hypertension, pyelonephritic contracted kidney and extraglomerular acute nephritis (1 case). The lowest rate of reabsorption was found in pyelonephritic contracted kidney.

The decrease in urea reabsorption, usually combined with disturbed filtration and reabsorption of water, may depend on two factors: the decrease in the urinary concentration and the presence of damage to the kidneys.

With severest damage to the kidneys the urea clearance may exceed the creatinine clearance. This may be interpreted as an indication of urea secretion.

Uremia due to reabsorption in renal disease does not exist. On the contrary, stronger antiosmotic forces are effective at the tubular barrier against the back flow of urea. This mechanism is probably compensatory in order to prevent urea retention with decreased filtration.

33. Fuchs, F., and Popper, H.: Ergebn. d. inn. Med. u. Kinderh. **54**:1, 1938.

Progress in Internal Medicine

BRIGHT'S DISEASE

A REVIEW OF RECENT LITERATURE

WILLIAM S. McCANN, M.D.
ROCHESTER, N. Y.

During the past year the major efforts of investigators in this field have been concentrated on the question of the renal factor in hypertension. The recent impetus to investigation has come from the work of Goldblatt, which has been discussed in previous reviews. As one might have supposed, search of the literature has brought to light prior discoveries of similar import which have been passed over and forgotten because their significance was not appreciated at the time they were made. Such discoveries in no way diminish the credit that is due Goldblatt, for, after all, they would have remained forgotten had it not been for the revival of interest aroused by his work.

In 1909 Theodore Janeway [1] published a brief note on the changes in blood pressure following the reduction of the renal arterial circulation. He observed the blood pressure of dogs before and after ligation of branches of the renal arteries by Alexis Carrel. Janeway used a modification of the Riva-Rocci sphygmomanometer. Rises in blood pressure were noted after the ligations. One of the 5 dogs which survived showed a rise of blood pressure from 110 to 150 mm. of mercury systolic and from 80 to 110 diastolic. The urine of this dog was free from albumin. Another of these dogs was observed to show a much greater rise in pressure, but the urine of this dog contained albumin, casts and red corpuscles.

Another instance in which search of the literature has brought forgotten work to light is to be found in the report of Tigerstedt and Bergmann,[2] who in 1898 discovered the pressor substance in the kidney and named it "renin." This substance, as originally described by these

From the Department of Medicine of the University of Rochester School of Medicine and Dentistry and the Medical Clinic of the Strong Memorial and Rochester Municipal Hospitals.

1. Janeway, T.: Note on Blood Pressure Changes Following Reduction of Renal Arterial Circulation, Proc. Soc. Exper. Biol. & Med. **6**:109, 1909.

2. Tigerstedt, R., and Bergmann, P. G.: Niere und Kreislauf, Skandinav. Arch. f. Physiol. **8**:223, 1898.

workers, appears to be identical with the pressor substance to which the hypertension of renal ischemia is now attributed.

Still another instance concerns the production of nephritis by the use of heterologous nephrotoxic serums, as recently described by Masugi and by Smadel. In 1900, however, Lindemann [3] produced a nephrotoxic serum from guinea pigs which had been given injections of emulsions of rabbit kidney. When injected into rabbits this serum produced profound disintegration of the renal tubules, no specific alteration of the glomeruli being observed. In this respect the experimental nephritis differed from that more recently described by Smadel, a condition which has proved to be true glomerular nephritis. Nevertheless, Lindemann deserves credit for the use of cytologic antiserums for the production of an experimental disease.

RENIN

To return to the question of the renal pressor substance, a number of investigators have been engaged in devising methods for the extraction and purification of renin. Tigerstedt and Bergmann had used simple saline extracts. They believed the pressor substance to be a protein. Boylston, McEwen and Ivy [4] were unable to obtain it by perfusion of ischemic kidneys with Locke's solution. However, Fasciolo, Houssay and Taquini [5] were able to demonstrate its presence in the blood of the renal vein by testing for vasoconstrictor effects on the toad Bufo arenarum Hensel. Saline extracts of ischemic dog kidneys and of kidneys of human subjects with hypertension were found to yield greater pressor effects than similar extracts of normal kidneys by Prinzmetal, Friedman and Abramson.[6] The blood of patients with hypertension when transfused into those with normal pressures did not exhibit any pressor effects, according to the observations of Friedman and Prinzmetal.[7] When saline extracts were subjected to pre-

3. Lindemann, W.: Sur le mode d'action de certains poisons rénaux, Ann. Inst. Pasteur **14**:49, 1900.

4. Boylston, G. A.; McEwen, E. G., and Ivy, A. C.: A Pressor Substance Is Not Present in the Perfusate of Ischemic Kidneys, Proc. Soc. Exper. Biol. & Med. **39**:559, 1938.

5. Fasciolo, J. C.; Houssay, B. A., and Taquini, A. C.: The Blood Pressure Raising Secretion of the Ischemic Kidney, J. Physiol. **94**:281, 1938.

6. Prinzmetal, M.; Friedman, B., and Abramson, D. I.: The Nature of Arterial Hypertension with Special Reference to the Role of the Kidney, Ann. Int. Med. **12**:1604, 1939.

7. Friedman, B., and Prinzmetal, M.: Vasomotor Effects of Blood in Patients with Hypertension and Animals with Experimental Hypertension, Ann. Int. Med. **12**:1617, 1939.

cipitation with ammonium sulfate, the pressor substance was found in the precipitate by Williams, Harrison and Mason.[8]

Highly purified preparations of renin have been made by Helmer and Page.[9] They believe the substance to be a protein. Color tests for guanidine groups and for pentose were especially strong. The purest preparations were found to elevate the blood pressure of dogs 30 mm. of mercury when given in amounts representing 0.027 mg. of nitrogen per kilogram of body weight. In cats it was three times as active, since 0.009 mg. per kilogram would produce the same rise in blood pressure as the larger dose in the dog. Swingle, Taylor, Collings and Hays [10] describe a method of purifying renin by saline extraction and ammonium sulfate precipitation, no organic solvents being used. The substance is stable if frozen or dried by the lyophile process. They define a renin unit as the minimum amount necessary, when given intravenously over a period of two to five seconds, to raise the mean blood pressure of anesthetized dogs an average of 40 mm. of mercury above the starting level. This unit is equivalent to 0.1 mg. of solid material per kilogram of body weight. The effects observed were proportional to the dose, up to 3 mg. per kilogram. Higher doses were found not to give proportionally greater effects. Renin was found to be nontoxic in doses up to 35 mg.

Atumi [11] describes a substance found in the blood of the renal veins which raises the blood pressure of normal rabbits and those having splanchnic sections. This substance is said to be soluble in ethyl alcohol, ether, chloroform and acetone. He believes it to be a sterol. Obviously this substance differs markedly from the renin just described.

As one might suppose, renin is being actively studied from the physiologic and pharmacologic standpoints. Page [12] and Merrill, Williams and Harrison [13] agree in their reports that the pressor effect is elicited by direct action on the blood vessels, a conclusion also reached

8. Williams, J. R., Jr.; Harrison, T. R., and Mason, M. F.: Observations on Two Different Pressor Substances Obtained from Extracts of Renal Tissue, Am. J. M. Sc. **195**:339, 1938.

9. Helmer, O. M., and Page, I. H.: Purification and Some Properties of Renin, J. Biol. Chem. **127**:757, 1939.

10. Swingle, W. W.; Taylor, A. B.; Collings, W. D., and Hays, H. W.: Preparation and Bioassay of Renin, Am. J. Physiol. **127**:768, 1939.

11. Atumi, Y.: Control of Blood Pressure by Nephrohormone, J. Chosen M. A. **29**:326, 1939; abstracted, Chem. Abstr. **33**:5055, 1939.

12. Page, I. H.: On the Nature of the Pressor Action of Renin, J. Exper. Med. **70**:521, 1939.

13. Merrill, A.; Williams, J. R., Jr., and Harrison, T. R.: The Site of Action of the Renal Pressor Substance, Am. J. M. Sc. **196**:18, 1938.

by Tigerstedt, and that it is little influenced by elimination of the nervous system, the hypophysis, the adrenal glands, the pancreas, the liver or the kidneys. The latter investigators found the action of renin to be heightened if the kidneys are removed two or three days before injection. Fasciolo, Houssay and Taquini [5] found that the presence of healthy kidneys is capable of diminishing the pressor effect of renin. They have also found that grafting an ischemic dog kidney into a dog from which both kidneys have been removed will elevate the blood pressure whether the adrenal glands have been removed or not, a result that is not in agreement with some earlier work. That some conflicting conclusions are reached by the various investigators who are studying renin is not surprising, since several methods of preparation are in use.

Page [12] has found that on giving successive injections of renin a diminishing pressor response is obtained. This fact was noted in Tigerstedt's original work. Page attributes this phenomenon to one or both of two causes, either to the progressive exhaustion of a renin activator or to the development of an antisubstance. In favor of the existence of a renin activator is the fact that no vasoconstrictor effect is observed when a rabbit's ear is perfused with pure renin dissolved in Ringer's solution. The activator is believed to be a protein-like substance present in normal blood, since the constrictive effect is obtained when a rabbit's ear is perfused with blood to which renin has been added. On successive additions of renin to this blood the renin activator appears to be exhausted. If the ear is perfused with fresh blood the constrictive response to the added renin is restored.

The effect of renin on the intrinsic circulation of the kidney itself has been studied by Merrill, Williams and Harrison.[15] These workers have been able to obtain two pressor substances from kidneys, one, renin, being obtained from the saline extract and the other, a tyramine-like substance, from autolysate. They found differences in the action of these two substances. When renin elevates the blood pressure, the kidney swells, the blood flow through it is decreased, and the volume of the urine is increased. This is interpreted as an indication that renin causes a constriction of the efferent arterioles of the glomerulus. On the other hand, tyramine was thought to constrict the afferent arterioles, since its action caused a shrinkage in volume of the kidneys and a diminution of renal blood flow.

---

14. Footnote deleted.

15. Merrill, A.; Williams, R. H., and Harrison, T. R.: The Effects of a Pressor Substance Obtained from the Kidneys on the Renal Circulation of Rats and Dogs, Am. J. M. Sc. **196**:240, 1938.

In a series of lectures given at the University of Kansas, Homer Smith [16] reviews his observations on the mechanism controlling renal blood flow. He has found that under ordinary circumstances the flow is chiefly regulated by variations in the tonus of the efferent glomerular artery. When this artery is constricted the blood flow is diminished; when it dilates, the flow is increased. Constriction of this arteriole has the effect of raising the filtration pressure within the glomerulus so that even when the blood flow is thus diminished the amount of glomerular filtrate tends to remain constant. Agents capable of causing constriction of the afferent glomerular arteriole would also have the effect of diminishing the total blood flow through the kidney, but in this case the expected result would be a diminution in the amount of glomerular filtrate as well. Smith believes that the control of the tonus of the efferent arteriole is independent of the connections of the kidney with the nervous system; hence a great measure of constancy of renal function may be achieved during wide variations in systemic blood pressure and blood flow, though it is obvious that extreme variations in the latter factors must have effects on the afferent blood supply to the kidney for which no intrinsic compensation could be made. Reference will be made subsequently to the application of this work to the study of hypertension in human subjects.

Corcoran and Page [17] observed that the slow intravenous infusion of renin elevated blood pressure, constricted the efferent glomerular arterioles and diminished renal blood flow, findings which are in agreement with those of others.[15] In contrast, similar infusion of pitressin produced variable effects on the renal blood flow and no effect on the systemic blood pressure.

The influence of sympathomimetic substances has received the attention of several investigators, with divergent results. Williams [18] found that the pressor effects of renin were enhanced by cocaine and inhibited by

16. (*a*) Smith, H. W.: Studies in the Physiology of the Kidney: I. Newer Methods of Study of Renal Function in Man; III. The Renal Blood Flow in Normal and Hypertensive Subjects, Publication of the University Extension Division, University of Kansas, Lawrence, Kan., 1939; (*b*) New Aspects of Renal Physiology, J. Urol. **41**:867, 1939. (*c*) Smith, H. W.; Rovenstine, E. A.; Goldring, W.; Chassis, H., and Ranges, H. A.: The Effects of Spinal Anesthesia on the Circulation in Normal, Unoperated Man with Reference to the Autonomy of the Arterioles, and Especially Those of the Renal Circulation, J. Clin. Investigation **18**:319, 1939.

17. Corcoran, A. C., and Page, I. H.: The Effects of Renin and Pitressin and Atropine on Renal Blood Flow and Clearance, Am. J. Physiol. **126**:354, 1939.

18. Williams, J. R., Jr.: The Effect of Cocaine and Ergotamine on the Action of the Renal Pressor Substance, Am. J. Physiol. **124**:83, 1938.

ergotamine. On the other hand, Katz and Friedberg [19] found that the quantitatively similar pressor action of renin in normal and in hypertensive dogs is not abolished by piperidomethylbenzodioxane, a substance which reverses the action of epinephrine in dogs and resembles the action of ergotamine in this respect. From this he concluded that renin does not act as a sympathomimetic substance.

The influence of various ductless glands on the action of renin is still somewhat confused. Fasciolo, Houssay and Taquini [5] noted that hypophysectomy diminished the blood pressure of dogs with renal ischemia. They observed that renin exerted its pressor effects in the absence of the adrenal glands. A small remnant of adrenal tissue will keep the blood pressure high in hypertensive dogs. Williams, Diaz, Burch and Harrison [20] found that rats which were kept alive after adrenalectomy by having salt administered to them were less sensitive to the action of renin, although their kidneys on assay did not contain less renin than the kidneys of normal rats. Rats after hypophysectomy were more sensitive to renin, their kidneys likewise yielding normal amounts of renin. Castration was found to have no effect on sensitivity to renin nor on the renin content of the kidneys.

Grossman and Williams [21] have studied the effect of age on the sensitivity to renin. Doses were given to rats of various ages in proportion to the body surface. Young rats, aged 6 to 10 weeks, showed the least rise in blood pressure, while the oldest rats, 2½ years of age, exhibited the greatest rise. The authors suggest that this effect of age on sensitivity to the action of renin may be one of the factors involved in the greater frequency of hypertension in old age.

EXPERIMENTAL URETERAL OBSTRUCTION

The effects of ureteral obstruction on the blood pressure have been receiving renewed attention. Blalock and Levy [22] credit Rautenberg, in 1910, with having been the first to observe hypertension following experimental ligation of the ureters. Harrison, Mason, Resnik and

19. Katz, L. N., and Friedberg, L.: The Hemodynamic Effect of the Dioxane Derivative 933F on Trained Unanesthetized Normal and Renal Hypertensive Dogs and Its Effect on the Pressor Action of Renin, Am. J. Physiol. **127**:29, 1939.

20. Williams, J. R., Jr.; Diaz, J. T.; Burch, J. C., and Harrison, T. R.: The Relation of the Adrenal Glands to the Action of the Renal Pressor Substance, Am. J. M. Sc. **198**:212, 1939.

21. Grossman, E. B., and Williams, J. R., Jr.: Relation of Age to Renal Pressor Substance, Arch. Int. Med. **62**:799 (Nov.) 1938.

22. Blalock, A., and Levy, S. E.: Studies on the Etiology of Renal Hypertension, Ann. Surg. **106**:826, 1937.

Rainey [23] have made similar observations. Pickering and Prinzmetal [24] did not observe hypertension following unilateral ligation of the ureters in 4 rabbits. Williams, Wegria and Harrison [25] found that unilateral ligation sometimes did and sometimes did not elevate the blood pressure. Even when no hypertension followed unilateral ligation, the sensitiveness to renin was increased. When hypertension was induced by unilateral ligation of the ureter, Blalock and Levy [22] were able to abolish it by removal of the hydronephrotic kidney. Rats with bilateral spontaneous hydronephrosis were found [25] regularly to exhibit hypertension, and such rats showed a much more pronounced pressor response to renin than did rats without hydronephrosis. These observations may have some bearing on the observations of Dill and Erickson,[26] who noted that slight renal ischemia, which was followed by no severe disturbance in nonpregnant dogs, caused fulminating eclampsia in pregnant dogs. Whether the physiologic hydronephrosis of pregnancy had an effect of increasing the sensitivity to renin has not been determined. There are of course, many other possible reasons which might be advanced in explanation of the eclampsia observed.

SECONDARY PHENOMENA IN EXPERIMENTAL HYPERTENSION

Gibson and Robinson [27] have observed the blood volume in dogs with hypertension induced by Goldblatt clamps on the renal arteries. Cardiac hypertrophy developed in all the animals. No constant trend of the blood volume was observed in these animals. Renal function was unimpaired. One dog with congestive heart failure was found to have an increase in blood volume.

It has long been thought that arteriolar sclerosis is a result rather than a cause of hypertension. The microscopic appearances of arte-

23. Harrison, T. R.; Mason, M. F.; Resnik, H., and Rainey, J.: Changes in Blood Pressure in Relation to Experimental Renal Insufficiency, Tr. A. Am. Physicians **51**:280, 1936.

24. Pickering, G. W., and Prinzmetal, M.: Experimental Hypertension of Renal Origin in the Rabbit, Clin. Sc. **3**:357, 1938.

25. Williams, J. R., Jr.; Wegria, R., and Harrison, T. R.: Relation of Renal Pressor Substance to Hypertension of Hydronephrotic Rats, Arch. Int. Med. **62**: 805 (Oct.) 1938.

26. (*a*) Dill, L. V., and Erickson, C. C.: Eclampsia-Like Syndrome Occurring in Pregnant Dogs and Rabbits Following Renal Artery Constriction, Proc. Soc. Exper. Biol. & Med. **39**:362, 1938. (*b*) Dill, L. V.; Isenhorn, C. E., and Cadden, J. F.: The Effect of Quantitative Reduction of Renal Blood Flow upon the Pregnant Rabbit, J. Clin. Investigation **18**:641, 1939.

27. Gibson, J. G., and Robinson, R. W.: Blood Volume, Cardiac Size and Renal Function in Dogs with Hypertension Produced by the Goldblatt Technic, Proc. Soc. Exper. Biol. & Med. **39**:497, 1938.

riolar lesions in "benign" hypertension have been contrasted with those occurring in "malignant" hypertension. Acute arteriolar lesions of the "malignant" variety have been found by Wilson and Pickering [28] in rabbits with experimental hypertension induced by partial constriction of the renal arteries. The incidence of these lesions is related to the degree of hypertension rather than to its duration. They were observed most frequently in the arterioles of the intestine, stomach, liver, adrenal glands, heart and eyes. The arterioles of the ischemic kidneys did not undergo these changes. In this respect the intrinsic circulation of the experimental animals employed (rabbits) differs from that commonly found in human subjects with "malignant" hypertension.

"ESSENTIAL" HYPERTENSION

Under the impact of the rapid accumulation of new facts regarding renal hypertension, the conception of "essential" hypertension is, of necessity, undergoing profound alterations. In the last review [28a] it was noted that clinical and pathologic reports were accumulating in illustration of the manner in which the condition of renal ischemia occurred in man. Further evidence is now available as to the importance of lesions affecting the patency of the large renal arteries. Blackman [29] reports the pathologic changes in 50 cases of "essential" hypertension as compared with the changes in a control series of 50 nonhypertensive subjects, balanced as to the incidence of age and sex. He found that in 86 per cent of the cases of hypertension the patients showed narrowing of the main renal arteries at or near the aorta. In 54 per cent the narrowing was pronounced, and in 32 per cent the lumen was narrowed to 1.5 mm. or less. In 14 per cent no significant narrowing was observed. In only 10 per cent of the controls was any narrowing of the renal arteries discovered. Leadbetter and Burkland [30] report the interesting case of a Negro boy 5½ years of age who had suffered from marked hypertension for three years. Operative removal of an ectopic kidney, the main renal artery of which was nearly occluded by a smooth muscle tumor, led to relief of the hypertension. Boyd and Lewis,[31] in the course

28. Wilson, C., and Pickering, G. W.: Acute Arterial Lesions in Rabbits with Experimental Renal Hypertension, Clin. Sc. **3**:343, 1938.

28a. McCann, W. S.: Bright's Disease: A Review of Recent Literature, Arch. Int. Med. **63**:590 (March) 1939.

29. Blackman, S. S.: Arteriosclerosis and Partial Obstruction of the Main Renal Arteries in Association with "Essential" Hypertension in Man, Bull. Johns Hopkins Hosp. **65**:353, 1939.

30. Leadbetter, W. F., and Burkland, C. E.: Hypertension in Unilateral Renal Disease, J. Urol. **39**:611, 1938.

31. Boyd, C. H., and Lewis, L. G.: Nephrectomy for Arterial Hypertension, J. Urol. **39**:627, 1938.

of bilateral exploration for an adrenal tumor, found a kidney in which there was a large infarct and marked arterial disease. The patient, a man of 31 years, had persistent elevation of blood pressure. Removal of the kidney was followed by a return of the blood pressure to normal range. Changes in the eyegrounds noted at the time of operation did not regress as the blood pressure fell. Blatt and Page [32] report finding a patient with hypertension whose renal arteries were constricted by a retroperitoneal tumor.

It has long been known to urologists that urinary obstruction is frequently associated with hypertension and that relief of the obstruction is commonly followed by lower blood pressure. An interesting study bearing on this point was made by Maher and Wosika,[33] who reviewed the records of 600 patients with hypertension. Of these, about one fifth had abnormalities of the urinary tract and kidneys, four fifths being left in the category of persons with "essential" hypertension. In the cases of urologic involvement with elevated blood pressure, prostatic hypertrophy was most frequent and chronic pyelonephritis next in frequency. The authors give a long list of other conditions in which various combinations of urolithiasis, obstruction and infection were present. Schroeder and Steele [34] made a study of "essential" hypertension in 71 young subjects who revealed no functional impairment of the kidneys. Intravenous pyelograms revealed abnormalities in 50 of the 71 patients. About one half of their patients had some form of urinary obstruction. In our clinic my associates and I have been greatly impressed with the frequency with which unsuspected obstruction and asymptomatic pyelonephritis are discovered in cases thought to be instances of "essential" hypertension. A report of these observations is in press.[35]

The complexity of the problem of trying to untangle the clues to the etiology of the disorders formerly grouped under the diagnosis of "essential" hypertension is well illustrated by the efforts of Schroeder and Steele [36] to classify 218 cases according to the clinical conditions associated with the hypertension. Five groups were made according to the predominant condition. In the renal group were 56 cases, with

32. Blatt, E., and Page, I. H.: Hypertension and Constriction of the Renal Arteries in Man: Report of a Case, Ann. Int. Med. **12**:1690, 1939.

33. Maher, C. C., and Wosika, P. H.: Urologic Hypertension: A Study of One Hundred and One Cases, J. Urol. **41**:893, 1939.

34. Schroeder, H. A., and Steele, J. M.: Abnormalities in the Urinary Tract in "Essential Hypertension," Proc. Soc. Exper. Biol. & Med. **39**:107, 1938.

35. McCann, W. S.: Chronic Pyelonephritis: A Cause of Hypertension and Renal Insufficiency, New York State J. Med., to be published.

36. Schroeder, H. A., and Steele, J. M.: Studies on "Essential" Hypertension: I. Classification, Arch. Int. Med. **64**:927 (Nov.) 1939.

14 cases of glomerulonephritis, 8 of calculus and 4 of pyelonephritis. In 29 cases there were the factors of stone, infection or obstruction, either alone or in combination. In 3 cases pregnancy was a factor. Similarly, in the other groupings, of nervous, endocrine, vascular and unclassified disorders, pregnancy appeared as a factor. A similar study has been made by Williams and Harrison,[37] with comparable results. It is obvious at this time that the term "essential hypertension" does not apply to any clinical entity. In view of the rapid progress of knowledge it will probably soon fall into entire disuse. At present it seems probable that in 80 to 85 per cent of these cases the condition depends on atheromatous narrowing of the larger renal arteries at or near the aorta and that in 15 to 20 per cent the trouble is due to unsuspected disorders of the kidneys or the urinary passages.

PYELONEPHRITIS

In previous reviews the growing interest in this subject has been recorded, in particular its relationship to hypertension and to the toxemias of pregnancy. The subject is thoroughly reviewed by Weiss and Parker,[38] with an extensive bibliography and a careful analysis of 100 cases. These authors confirm the original thesis of Wilson and Schloss, that pyelitis never exists without pyelonephritis. The extreme variability of the clinical course is emphasized. The infection may heal in a short time, or it may persist in a chronic form with either continuous or intermittent activity of the infection. The description of the morphologic changes observed in the kidneys of 100 patients is most complete and emphasizes several points, namely, the involvement of the lymphatic system of the kidneys and the variety of vascular changes observed. It is particularly noteworthy that in unilateral pyelonephritis the vascular lesions may be confined to the affected side. With such unilateral involvement hypertension may or may not be observed. The vascular lesions are similar to the severe obliterative lesions found in malignant nephrosclerosis. Weiss and Parker estimate that in 15 to 20 per cent of the cases "malignant" hypertension is due to pyelonephritis.

Encephalopathy, neuroretinitis and left ventricular failure with cardiac asthma were frequently observed in cases of hypertension due to pyelonephritis. However, organic diseases of the cerebral and coronary vessels appear to have occurred less frequently than in hypertensions of other origin. The vascular lesions of chronic pyelonephritis

37. Williams, J. R., Jr., and Harrison, T. R.: Clinical Pictures Associated with Increased Blood Pressure: A Study of One Hundred Patients, Ann. Int. Med. **13**:650, 1939.

38. Weiss, S., and Parker, F., Jr.: Pyelonephritis: Its Relation to Vascular Lesions and to Arterial Hypertension, Medicine **18**:221, 1939.

were found to be mainly restricted to the kidneys, in contrast to those of "primary" malignant hypertension, which are generalized.

Pyelonephritis was found rarely to coexist with glomerulonephritis. In pyelonephritis glomerular changes are observed, but these may be distinguished from those occurring in glomerulonephritis. The chronic and healed forms of the disease are more frequent than glomerulonephritis.

Pyelonephritis may complicate polycystic kidneys, hydronephrosis and tuberculosis of the kidneys. The vascular lesions characteristic of pyelonephritis did not occur in tuberculosis of the kidneys or in hydronephrosis which was uncomplicated by it.

Weiss and Parker believe that the hypertension of pyelonephritis is due to renal ischemia. This belief is presumably based on the character of the vascular lesions induced by this type of inflammatory process in the kidneys and the constrictive character of the interstitial fibrosis leading to contraction of the kidney. These authors emphasize the implications of the knowledge of this condition in the practice of preventive medicine. Since pyelonephritis is the one form of renal disease that can be successfully treated in its initial stages, a charge is laid on the conscience of every physician who encounters it to nip it in the bud so that its disastrous sequelae may be avoided.

GLOMERULONEPHRITIS

The experimental production of glomerulonephritis by means of nephrotoxic serums of heterologous origin has provided no explanation of the pathogenesis of the disease as it occurs in man. Some recent observations of Schwentker and Comploier [39] are illuminating in this respect. Rabbits were given injections of emulsions of homologous kidneys, alone and in combination with streptococcus toxin or staphylococcus toxin. There were also controls which received the toxins alone. In the blood of rabbits which had received injections of both the kidney emulsion and one or the other toxin, complement-fixing antibodies were found, one specific for kidney tissue and one nonspecific, in that it could be absorbed by the brain. Similar complement fixations were obtained with the blood of a majority of patients with scarlet fever. In only a few instances did the blood of normal patients exhibit this phenomenon. This work suggests that cytotoxins originate autogenously when the kidney is injured by toxins. It does not explain, however, why it is that in some persons clinically recognizable nephritis develops after scarlet fever while it does not develop in others.

39. Schwentker, F. F., and Comploier, F. C.: The Production of Kidney Antibodies by Injection of Homologous Kidney Plus Bacterial Toxins, J. Exper. Med. **70**:223, 1939.

Concerning the optimal amount of protein to be given in the diet of patients with glomerulonephritis, there has been considerable divergence of opinion. In recent years the trend of opinion in clinical circles has been definitely in favor of greater liberality, with some dissenting voices. Cameron [40] has reviewed the evidence in favor of a liberal ration of protein. From his own experience he recommends only temporary and moderate restriction during the initial and terminal stages. Under other circumstances he advocated a basic ration of 70 to 80 Gm. per day, to which should be added the equivalent of the protein lost in the urine.

There have come from experimental laboratories certain observations which call for careful consideration and evaluation by clinicians. Smadel and Farr [41] have observed the effect of the amount of protein in the diet on the course of experimental nephrotoxic nephritis in rats. These rats were divided into groups receiving low, medium and high protein diets (4, 14 and 32 per cent of the total number of calories, respectively). In those rats of the Whelan strain receiving low protein diets there was clinical and pathologic evidence that the disease subsided rapidly. The acute tubular injury resolved without permanent damage, and only moderate residual changes were noted in the glomeruli. In contrast, the disease progressed rapidly to renal failure in those receiving high protein diets. In more than half of the rats receiving medium protein diets renal failure developed, the general results being similar to those obtained in rats on a mixed stock diet.

One of the most significant effects observed in rats receiving the high protein diets is obliterative scarring of the tubules, with general evidence of epithelial injury of the kidneys. The diets given were isocaloric, the low protein diets being high in carbohydrate and the high protein diets low in carbohydrate. The question therefore rises in my mind as to whether or not the tubular injury may have been due rather to the lack of the protective action of carbohydrate against toxic injury, an action analogous to that exerted by carbohydrate in the liver. This would explain one discrepancy between these findings and the clinical observations made by my associates and me in our clinic, since the diets given there, which seemed not to exert any harmful effect, were liberal in the use of carbohydrate as well as of protein.[42]

---

40. Cameron, J. D. S.: Protein in the Treatment of Nephritis, Edinburgh M. J. **46**:386, 1939.

41. Smadel, J. E., and Farr, L. E.: The Effect of Diet on the Pathological Changes in Rats with Nephrotoxic Nephritis, Am. J. Path. **15**:199, 1939. Farr, L. E., and Smadel, J. E.: The Effect of Dietary Protein on the Course of Nephrotoxic Nephritis in Rats, J. Exper. Med. **70**:615, 1939.

42. McCann, W. S.: The Many Sided Question of Protein in Nephritis, Ann. Int. Med. **5**:579, 1931. Keutmann, E. H., and McCann, W. S.: Dietary Protein in Hemorrhagic Bright's Disease, J. Clin. Investigation **9**:973, 1932.

In a later paper Smadel and Swift [43] note the fact that the Whelan strain and the Evans strain of rats react differently as to the effect of the nephrotoxic serum and diet. In the latter rats the nephritis tended to subside rapidly and independently of the character of the diet. The greater susceptibility to the deleterious effects of protein may be a peculiarity of the Whelan strain.

Further light is thrown on this question of the dietary protein by Addis and Lew [44] and Bergman and Drury,[45] who have arrived independently at the same conclusion, namely, that the deleterious effect of meat protein is due to the high content of potassium. The former investigators produced anuria and a great increase in blood urea by ligation of the vena cava just above the point of entry of the renal veins. In groups of 40, rats were given diets designed to induce wide variations in protein consumption and catabolism. None of the animals died when given diets which were low in protein or which included moderate amounts of milk and cereal protein. With diets of dried yeast and casein no deaths occurred. When the intake of protein was large, including dried liver, kidney and beef, the mortality of the groups of rats was 8, 9 and 16 per cent, respectively. A water extract of the meat gave a 52 per cent mortality, while an alcohol-soluble extract gave none. Solutions of potassium acid phosphate (KH_2PO_4) and chloride caused the same mortality rate among the rats as did the water extract.

Bergman and Drury observed that the survival time after bilateral nephrectomy could be made very uniform under standard conditions. If sugar was given to the rats the survival was prolonged. If meat was given it was shortened. The urine of meat-fed rats was deleterious, and this effect was believed to be due to the high potassium content of this urine.

If the foregoing observations and interpretations are correct, the amount of protein may prove to be not as important as its source. Milk proteins may be less objectionable from the standpoint of having less potassium. One may also speculate as to whether the toxic effects of potassium might not be removed if there were a proper balance of other mineral substances, such as calcium and sodium. These questions are not answered in the studies just referred to.

---

43. Smadel, J. E., and Swift, H. F.: The Effect of Prolonged Administration of Sulfanilamide on Rats with Nephrotoxic Nephritis, J. Clin. Investigation **18**:757, 1939.

44. Addis, T., and Lew, W.: Diet and Death in Acute Uremia, J. Clin. Investigation **18**:773, 1939.

45. Bergman, H. C., and Drury, D. R.: A Study of Acute Renal Insufficiency. J. Clin. Investigation **18**:777, 1939.

A series of papers by Chanutin and Ludewig [46] appear to have somewhat the same import as those of Bergman and Drury, except that the deleterious effects were not attributed to potassium.

The nature of the arteriolar tonicity in acute glomerulonephritis has been studied by Arnott and Matthew,[47] the heat elimination from one hand being used as a measure of the blood flow through the hand. When the other hand was immersed in cold water the elimination of heat of the immersed hand was greater than normal, and this was taken as an indication of an increased blood flow. These observations were in confirmation of some previous work by Pickering, who found the blood flow normal in chronic hypertension and increased in acute hypertension under the conditions described. These observations recall the work of Landis, Montgomery and Sparkman, which has been previously reviewed; their work showed that the action of renin is unlike that of other pressor substances in that it does not decrease the temperature of the skin.

The hypertension of glomerulonephritis has been shown by Hayman, Martin and Miller [48] to bear little relationship to the number of patent glomeruli. For a number of years Hayman has employed a method of estimating the number of glomeruli remaining patent. In the most recent study it was found that when less than 700,000 glomeruli per kidney were patent the systolic blood pressure was 150 or more. Below this critical level there was no correlation with the count of glomeruli, and elevation of blood pressure was observed in instances in which there was little or no reduction in the count. However, if the maximum concentration of the urine is considered, one again finds a critical decrease in concentrating power at about 700,000 glomeruli per kidney. Below that level the maximum specific gravity is 1.010. When hypertension occurs in glomerulonephritis, together with low concentrating power, one may suppose that the number of patent glomeruli are less than 700,000 per kidney; and if the maximum concentration is in normal limits, more than this number of glomeruli are patent. Hayman points

46. Chanutin, A., and Ludewig, S.: Experimental Renal Insufficiency Produced by Partial Nephrectomy: XI. Diets Containing Dried Extracted Liver, Arch. Int. Med. **64**:513 (Sept.) 1939; XII. Diets Containing Dried Extracted Meat, ibid. **64**:526 (Sept.) 1939; XIII. A Summary of the Effect of Whole Liver, Whole Meat, Extracted Liver and Extracted Meat Diets on Renal Hypertrophy, Renal Function, Blood Pressure, and Cardiac Hypertrophy, ibid. **64**:747 (Oct.) 1939; XIV. Diets Containing Whole Dried Yeast, ibid. **64**:756 (Oct.) 1939.

47. Arnott, W. M., and Matthew, G. D.: The Nature of the Arteriolar Hypertonicity in Acute Glomerulo-Nephritis, Quart. J. Med. **8**:353, 1939.

48. Hayman, J. M., Jr.; Martin, J. W., Jr., and Miller, M.: Renal Function and the Number of Glomeruli in the Human Kidney, Arch. Int. Med. **64**:69 (July) 1939.

out that the degree of functional impairment in the glomeruli may be greater than the degree of damage revealed in the histologic preparations. It was found that in certain cases of acute infections and jaundice clearance and concentrating ability may be markedly reduced in spite of a normal number of glomeruli showing no significant change in the histologic sections.

INTERCAPILLARY GLOMERULOSCLEROSIS

In 1936 a syndrome was described by Kimmelstiel and Wilson,[49] consisting of diabetes, albuminuria, hypertension, retinal vascular changes and a nephrotic syndrome, and some degree of renal insufficiency was found to be associated with a peculiar intercapillary glomerulosclerosis. A number of cases of this syndrome have been collected and are further described by Newburger and Peters.[50] In the glomeruli, hyaline deposits are laid down between the basement membrane and the epithelium. Amyloid is to be excluded. The picture is not to be confused with intercapillary fibrosis, which sometimes occurs in glomerulonephritis and may be recognized by special stains of the basement membrane. The authors regard the condition as a clinical entity which depends on severe and extensive arterial and arteriolar degeneration associated with and perhaps resulting in diabetes and renal damage.

THE NEPHROSES

Support for the idea that there is a genuine lipoid nephrosis, as distinguished from a nephrotic stage of glomerulonephritis, is strongest in pediatric circles. Bearing on a peculiar metabolic disturbance in the nephroses of children are some important observations of Farr.[51] He observed that the nitrogen balance of 2 children with the nephrotic syndrome showed marked spontaneous changes which preceded clinical evidences of increased severity of the syndrome. Mild infections of the upper respiratory tract tend to produce negative nitrogen balances, with failure to assimilate nitrogen and increased proteinuria. Nephrotic crises occur which are not uniformly accompanied by an increase in nitrogen loss. Such episodes reflect an acute disturbance in a patient chronically manifesting evidence of inability to assimilate protein.

49. Kimmelstiel, P., and Wilson, C.: Intercapillary Lesions in the Glomeruli of the Kidney, Am. J. Path. **12**:83, 1936.

50. Newburger, R. A., and Peters, J. P.: Intercapillary Glomerulo-Sclerosis: A Syndrome of Diabetes, Hypertension, and Albuminuria, Arch. Int. Med. **64**: 1252 (Dec.) 1939.

51. Farr, L. E.: Assimilation of Protein by Young Children with Nephrotic Syndrome: III. Effect of Nephrotic Crises on Assimilation of Nitrogen, Am. J. Dis. Child. **58**:939 (Nov.) 1939.

Farr [52] also notes that when these children are on a fixed nitrogen intake varying the proportions of fat and carbohydrate has no effect on the nitrogen balance.

In the nephroses of children Farr and Van Slyke [53] find that edema can be controlled satisfactorily in most instances by simple restriction of salt, together with an adequate diet, when the plasma albumin concentration is above 1.2 Gm. per hundred cubic centimeters. This concentration is decidedly below that of 2.5 Gm. per hundred cubic centimeters found for adults in their clinic.

MacLeod and Farr [54] discuss the unusual susceptibility of nephrotic children to pneumococcic peritonitis. The attacks of this infection are usually due not to freshly acquired organisms but to an organism carried for some time, which invades when the resistance is lowered by some metabolic disturbance, such as the acute nephrotic crises previously described.

The observations of Major [55] on the treatment of lipoid nephrosis show that the best results were obtained by the use of high carbohydrate diets, blood transfusions and diuretics. Administration of an anterior pituitary extract (antuitrin G), choline (hydroxyethyltrimethylammonium hydroxide) and adrenal cortex extract had no appreciable effect on the course of the disease, although in some instances the ingestion of choline seemed to lower the content of blood cholesterol.

Yuile and Knutti [56] report experiments on the use of acacia which should further discourage those who would rashly use this substance in the management of the edema of nephrosis. When weekly intravenous injections of acacia were repeated for four or five months, it was found possible to maintain the concentration of plasma protein and of total circulating protein at a low level. When the injections were stopped the effect continued for several months more, during which the acacia remained in the blood. That the fibrinogen of the plasma was reduced out of proportion to the other proteins indicated an effect on the liver. Plasma volume decreased at first and then

52. Farr, L. E.: Assimilation of Protein by Young Children with Nephrotic Syndrome, Am. J. Dis. Child. **58**:935 (Nov.) 1939.

53. Farr, L. E., and Van Slyke, D. D.: Relation Between Plasma Protein Level and Edema in Nephrotic Children, Am. J. Dis. Child. **57**:306 (Feb.) 1939.

54. MacLeod, C. M., and Farr, L. E.: Relation of the Carrier State to Pneumococcal Peritonitis in Young Children with Nephrotic Syndrome, Proc. Soc. Exper. Biol. & Med. **37**:556, 1937.

55. Major, R. H.: Observations on the Treatment of Lipoid Nephrosis, Ann. Int. Med. **12**:1555, 1939.

56. Yuile, C. L., and Knutti, R.: Blood Plasma Proteins as Influenced by Intravenous Injection of Gum Acacia: II. Production of Chronic Hypoproteinemia, J. Exper. Med. **70**:605, 1939.

increased to a value 20 to 24 per cent above basal levels, but the total blood volume did not increase since there was a decrease in cell volume. These observations appear to me as highly important, since they indicate that the injection of acacia may actually interfere with the regeneration of plasma protein through interference with hepatic function.

The early recognition of renal amyloidosis in tuberculous patients is discussed by Altnow, Van Winkle and Cohen.[57] In a majority of the cases studied the onset could be dated with reasonable accuracy from some clinical event, such as the onset of enteritis, pleural effusion, empyema, or other suppuration, the institution of pneumothorax or some other surgical procedure. In the greater number of patients amyloidosis developed in association with enteritis, or in association with pleuritis, peritonitis or pericarditis, alone or in combination. If the diagnosis were to be made only on the observation of suppurative lesions in association with enlargement of the liver and spleen, the great majority of the cases would be missed. Hyposthenuria was the most constant single finding.

Concerning renal disease in syphilis Baker[58] makes an interesting report. It appears that there is a not infrequent type of nephrotic lesion to be observed in the kidneys of those dying with syphilis. This has been described by Rich and also by Bauer. Occasionally this condition may be manifest as a clinical nephrosis, and in cases of this type as well as in those of hemorrhagic nephritis occurring in syphilitic patients, lesions may heal under antisyphilitic therapy. In the cases of hemorrhagic nephritis healing may be produced by the closing over of ulcers of the upper respiratory tract, through which infection may have entered to give rise to the nephritis. There remains the possibility that the spirochetes may be capable of exciting either a nephrosis or a nephritis. The effect of therapy is suggestive but not conclusive.

Smetana[59] describes the clinical events and the pathologic changes occurring in patients in whom a nephrosis develops after the inhalation of carbon tetrachloride. In addition to hepatic damage the renal symptoms consist of oliguria or anuria, azotemia and subsequent hypertension and the presence in the urine of albumin, leukocytes, red cells, casts and bile. Histologically, the kidneys reveal a distention of Bowman's capsule by an albuminous precipitate and swelling of the

57. Altnow, H. O.; Van Winkle, C. C., and Cohen, S. S.: Renal Amyloidosis: A Further Study of the Clinical Course and Pathological Lesions in Fifty-Seven Cases, Arch. Int. Med. **63**:249 (Feb.) 1939.

58. Baker, B. M., Jr.: The Relation of Syphilis to Nephritis, Bull. Johns Hopkins Hosp. **65**:196, 1939.

59. Smetana, H.: Nephrosis Due to Carbon Tetrachloride, Arch. Int. Med. **63**:760 (April) 1939.

lining cells, by swelling and vacuolation of the proximal tubular epithelium and by degeneration and necrosis of the distal tubular cells and Henle's loop, with desquamation and plugging of the tubules. Concretions are present, the nature of which remains obscure.

Much has been written about the renal complications of multiple myeloma. Some recent observations of Ulrich [60] indicate that in some cases hydronephrosis occurs as a result of obstruction of the tubules by casts of Bence-Jones protein. In other cases the mechanism is not known.

PHYSIOLOGIC STUDIES

Homer Smith and his collaborators [61] have extended their studies of the renal circulation to determine the effects of high spinal anesthesia. When this is carried to levels considerably above those at which the sympathetic pathways to the kidneys emerge from the cord, renal hyperemia was not observed, nor was there any consistent effect on the renal circulation. This confirmed their view that the tonus of the renal arterioles is normally maintained by the autonomous intrinsic activity of the peripheral vascular apparatus and that it is not dependent on the activity of the central nervous system.

In work previously reviewed, Smith and his colleagues estimated that the normal renal blood flow as measured by the diodrast clearance is in the neighborhood of 1,340 cc. per minute for a man of 1.73 square meters of body surface. Chesley and Chesley [62] present data which indicate that the estimates arrived at by Smith are too high. In a group of normal women they found the renal blood flow to be 879 cc. per minute, the flow being 856 cc. in a group of pregnant women. They suggest that the higher result obtained by Smith was due to the fact that the diodrast was given in the same infusion with inulin, phenolsulfonphthalein and sometimes sodium sulfate. They point out that Herrick, Mann and Sheehan [63] found that phenolsulfonphthalein and creatinine alter the renal blood flow as measured by a thermostrohmuhr.

Chesley and Chesley also calculate that the renal blood flow of other animals is 3.2 to 3.3 cc. per gram of kidney. Estimating the average

60. Ulrich, H.: Multiple Myeloma, Arch. Int. Med. **64**:994 (Nov.) 1939.

61. Smith, H. W.; Rovenstine, E. A.; Goldring, W.; Chassis, H., and Ranges, H. A.: The Effects of Spinal Anesthesia on the Circulation in Normal, Unoperated Man with Reference to the Autonomy of the Arterioles, and Especially Those of the Renal Circulation, J. Clin. Investigation **18**:319, 1939.

62. Chesley, L. C., and Chesley, E. R.: The Diotrast Clearance and Renal Blood Flow in Normal, Pregnant and Non-Pregnant Women, Am. J. Physiol. **127**:731, 1939.

63. Herrick, J. F.; Mann, F. C., and Sheehan, H. L.: The Influence of Phenol Red and Creatinine on the Renal Blood Flow, J. Pharmacol. & Exper. Therap. **66**:73, 1939.

weight of the kidney in women studied, they believe that their results are more in keeping with this figure than are those of Smith. On the basis of mean kidney weight they would expect a total renal blood flow of 1,080 cc. in men.

Chesley also comments on the variability of the proteinuria in the hypertensive toxemias of pregnancy.[64] The concentration of protein in the filtrate is calculated from that of the urinary protein by assuming it to be proportional to the ratio of the urinary creatinine to the endogenous creatinine. He found that the amount of protein filtered varies little from hour to hour in nephritic patients, in contrast to a great variability in women with toxemia, which he takes as an indication that the proteinuria is due to vascular spasm in such cases. It would seem unwise to accept this work without some reservations, especially in view of the possibility that some of the urinary protein may come from the tubules, just as some of the creatinine has been found to be secreted rather than filtered.

The blood volume in Bright's disease has been measured by Harris and Gibson.[65] The plasma volume was found to vary directly as the albumin and nonprotein nitrogen concentrations of the serum, and to vary inversely as the degree of anemia. The interrelation of the plasma and red cell volumes was such that the total blood volume was below normal in all stages of the disease. When congestive heart failure was present the volume was greater than it would have been without it. The circulation time was also observed to be prolonged in the nephrotic syndrome.

Smith [16a] estimates that the normal tubules have the capacity of resorbing dextrose to a maximum capacity of 320 mg. per minute, and he points out that the renal threshold is to be conceived in terms of maximal resorptive capacity rather than in terms of plasma dextrose concentration. Govaerts and Muller [66] have studied the mechanism of dextrose excretion by the kidney in the diabetic dog. They take the creatinine clearance as the measure of the glomerular filtration and estimate the concentration of dextrose in the filtrate from the arterial plasma. In this way they estimate the amount of dextrose filtered per minute. As the value of blood sugar rises, the amount of dextrose resorbed increases to a maximum above which it does not increase no

64. Chesley, L. C.: The Variability of Proteinuria in the Hypertensive Complications of Pregnancy, J. Clin. Investigation **18**:617, 1939.

65. Harris, A. W., and Gibson, J. G., Jr.: Clinical Studies of Blood Volume: VII. Changes in Blood Volume in Bright's Disease With or Without Edema, Renal Insufficiency, or Congestive Heart Failure, and in Hypertension, J. Clin. Investigation **18**:527, 1939.

66. Govaerts, P., and Muller, P.: The Mechanism of Glucose Excretion by the Kidney in Diabetic Dogs, J. Clin. Investigation **18**:25, 1939.

matter how high the value of the blood sugar. In 1 dog the threshold was thus found to be 390 mg., and in another, 347 mg. Similar studies were carried out in a case of diabetic coma reported by McCance and Widdowson.[67] The urine contained only 13 mg. of dextrose when the plasma sugar was 550 mg. per hundred cubic centimeters, and the inulin clearance (filtrate) was 125 cc. per minute. This would indicate a "threshold" or resorption of 670 cc. per minute, a value greatly in excess of normal.

The effect of the adrenal glands on the excretion of sodium and potassium has been investigated by Harrison and Darrow.[68] They found that after adrenalectomy the tubules failed to resorb sodium when the plasma sodium concentration was low and that they failed to excrete potassium when the plasma concentration of this substance was high.

In patients with essential and malignant hypertension de Wesselow and Thomson[69] found the serum potassium concentration to be lower than in normal persons on the same diet, and it was lower in persons with malignant hypertension than in persons with benign hypertension. Low levels of plasma sodium were not infrequently observed in patients with malignant hypertension. The administration of sodium salts was found to raise the blood pressure in patients with hypertension, while potassium salts were found to have the opposite effect. These alterations are slight and require amounts beyond the ordinary range found in the diet. Attempts to deplete the sodium content of the body were without effect.

MISCELLANEOUS

Lindberg, Wald and Barker[70] have found that the intravenous use of concentrated solutions containing 50 per cent of sucrose may produce transient reversible changes in the tubules and glomeruli of dogs. If the injections are often repeated the changes are more marked and may require a longer time for restitution or may even result in permanent alterations. No such changes occurred after similar use of 50 per cent solutions of d-sorbitol, 50 per cent solutions of dextrose or 10 per cent solutions of sodium chloride.

---

67. McCance, R. A., and Widdowson, E. M.: Functional Disorganization of the Kidney in Disease, J. Physiol. **95**:36, 1939.

68. Harrison, H. E., and Darrow, D. C.: Renal Function in Experimental Adrenal Insufficiency, Am. J. Physiol. **125**:63, 1939.

69. de Wesselow, O. L. V. S., and Thomson, W. A. R.: A Study of Some Serum Electrolytes in Hypertension, Quart. J. Med. **8**:361, 1939.

70. Lindberg, H. A.; Wald, M. H., and Barker, M. H.: Renal Changes Following Administration of Hypertonic Solutions (50 Per Cent Sucrose, 50 Per Cent D-Sorbitol, 50 Per Cent Dextrose, and 10 Per Cent Sodium Chloride), Arch. Int. Med. **63**:907 (May) 1939.

The effect of alcohol on the kidneys of normal persons and on those of patients with Bright's disease has been studied by Bruger, Localio and Guthrie,[71] who report that alcohol or whisky rarely augments the proteinuria of Bright's disease. Marked diuresis may follow its use even when the renal function is badly impaired. No deleterious effects were observed in normal subjects. In patients with nephrosclerosis there was sometimes observed to be a transient increase in the number of formed elements and a depression of function.

In some instances patients receiving sulfapyridine were found by Southworth and Cooke [72] to suffer from hematuria, abdominal pain and nitrogen retention. This condition was attributed to the effects of the drug, since it cleared when the drug was withheld. Antopol and Robinson [73] observed the formation of uroliths in rats, rabbits and monkeys to whom sulfapyridine was given. The uroliths were formed by needle-like crystals of the acetyl derivative and were located most frequently at the level of the brim of the pelvis. They were not radiopaque, though calcium deposits were sometimes found about them. Toomey [74] has confirmed these reports of finding large concretions in the bladder, ureters and pelvis of the kidneys, which were hyperemic and enlarged and sometimes the seat of pyelonephritis. He warned against the use of sulfapyridine in the presence of nephritis and urinary retention, and in particular he warned against its use in poliomyelitis, since it has no effect in this infection.

Smadel and Swift [43] found sulfanilamide to be without deleterious effects on the course of experimental nephrotoxic nephritis.

A new method of producing renal ischemia and experimental hypertension has been devised by Page,[75] who induced proliferative perinephritis as a reaction to enclosing the kidneys in cellophane. Removal of the kidney so affected cured the hypertension. Denervation of the kidney does not prevent the occurrence of hypertension. He suggested that perinephritis may be an additional cause of hypertension in man.

71. Bruger, M.; Localio, S. A., and Guthrie, N. W.: Effect of Alcohol on Normal Kidney and the Kidney of Bright's Disease, J. A. M. A. **112**:1782 (May 6) 1939.

72. Southworth, H., and Cooke, C.: Hematuria, Abdominal Pain, and Nitrogen Retention Associated with Sulfapyridine, J. A. M. A. **112**:1820 (May 6) 1939.

73. Antopol, W., and Robinson, H.: Urolithiasis and Renal Pathology After Oral Administration of Sulfapyridine, Proc. Soc. Exper. Biol. & Med. **40**:428, 1939.

74. Toomey, J. A.: Urinary Concretions and Sulfapyridine, J. A. M. A. **113**:250 (July 15) 1939.

75. Page, I. H.: Production of Arterial Hypertension, J. A. M. A. **113**: 2046 (Dec. 2) 1939.

Book Reviews

Clinical Gastroenterology. By Horace Wendell Soper, M.D., F.A.C.P. Cloth. Price, $6. Pp. 314, with 212 illustrations. St. Louis: C. V. Mosby Company, 1939.

This book is printed on an excellent quality of paper; the type is better than average, and the illustrations are generally good. Unfortunately, the material contained in the book does not measure up to the standards set by the publisher.

The author discusses diseases of the gastrointestinal tract. He includes, of course, diseases of the liver and biliary system and the pancreas. The content is principally the author's personal opinions and is mainly the result of his own large experience. Nothing particularly new is offered, although many portions of the book may be called novel. The advice that granulocytopenia be treated by intensive administration of neoarsphenamine will cause many hematologists to shudder. Arsenic is under consideration as a cause of neutropenia, not as a cure.

The tirade against milk is an example of wishful, but hardly scientific, reasoning.

The discussion of the various dyspepsias (a poor term at best) leaves the reader confused and baffled. Another baffling chapter is the one on indicanuria. The reader is left with the conclusion that "indicanuria (and such symptoms as may be attributed to it) is amenable to general and hygienic treatment, but the reaction in the urine remains four-plus regardless of the improvement in the patient's condition."

The chapter on disease of the liver and of the gallbladder is totally inadequate. The pancreas is considered in two and one-half pages, one page of which deals with diabetes mellitus.

This list of examples, which could be extended, leaves the reader with the impression that the book was rather carelessly put together and that there was a lack of critical judgment in the preparation of the material. This impression is augmented by the appearance of poor English: "Diagnosis is of extreme importance as they are very amenable to operative treatment." This remark, set out as a separate sentence, is a little difficult to interpret. Colloquialisms are used with too great frequency. "The monkey wrench in the works" is understandable to the American reader but might not be so readily translated or understood by one whose education did not include the use of American slang.

Altogether the book has little to recommend it to the critical reader.

Chirurgie der Lungen und des Brustfelles. By Alfred Brunner. Price, 24 marks. Pp. 277. Dresden: Theodor Steinkopff, 1938.

This twenty-sixth volume of the "Medizinische Praxis" series is concerned primarily with the surgical diseases of the lung and pleura. Its purpose is the succinct compilation and presentation for the practicing physician of the material on surgical management of the commoner diseases of the lung and pleura. Accordingly, it succeeds in being a compendious review of these conditions. Obviously, completeness in respect to details must be sacrificed.

Among the conditions considered by the author are abscess and gangrene of the lung, bronchiectasis, pulmonary tuberculosis, empyema, tumors, parasitic diseases and fungous infection of the lung and pleura. The well established indications and rationale of the various methods of conservative and operative management of these conditions are discussed. Appropriately, the greatest amount of space is devoted to tuberculosis. The indications and various technics of collapse therapy are briefly described. In this regard better illustrations of the operative

technic of extrapleural thoracoplasty are considered desirable. There is an excellent author and subject index, and the incomplete but fairly representative indexed bibliography is helpful.

Les maladies de l'oesophage. By J. Terracol, Professor of the Faculty of Medicine of the University of Montpellier. Price, 220 francs. Pp. 664, with 352 illustrations. Paris: Masson et Cie, 1938.

This book by Terracol, written with the collaboration of 16 other persons interested in various fields of the subject, includes a detailed discussion of the diseases of the esophagus. The subject is presented in the usual fashion, including a discussion of anatomy, physiology and methods of study, such as the endoscopic technics and roentgenology, clinical syndromes of esophageal dysfunction and therapy. The subject is presented clearly and completely, with much space devoted to endoscopic procedures for study and therapy. The book is well illustrated, having 352 figures in all. At the end of each chapter there is appended a fairly large bibliography, which is almost entirely European, especially French.

This monograph represents much work and should prove to be of considerable value to those interested in gastroenterology and endoscopic procedures on the esophagus and to the internist, surgeon and roentgenologist, who frequently desire a book containing an accumulation and evaluation of the literature on the subject of diseases of the esophagus.

Surgical Anatomy. By C. Latimer Callander, M.D., F.A.C.S. Second edition. Price, $10. Pp. 858, with illustrations. Philadelphia: W. B. Saunders Company, 1939.

The second edition of Callander's book on surgical anatomy is essentially the same as the first. In deleting discussions and illustrations which were out of date, the author has shortened the book by approximately 250 pages. Additions were made to include more recent advances in surgical anatomy, especially pertaining to surgery of the sympathetic nerves, syndromes involving the scalenus anticus muscle and cervical rib and the like. The book retains its lucid and practical features and should continue to be well received by surgeons.

News and Comment

American Board of Internal Medicine, Inc.—The American Board of Internal Medicine will conduct oral examinations previous to the meeting of the American College of Physicians in Cleveland and to the meeting of the American Medical Association in New York.

Applicants who have successfully passed the written examination and who plan to take the oral examination in 1940 should advise the office of the secretary at least six weeks in advance of the date of the examination they desire to take.

The next written examination will be given on October 21. Applications for this examination must be filed in the secretary's office by September 1.

Application forms may be obtained from Dr. William S. Middleton, secretary-treasurer, 1301 University Avenue, Madison, Wis.